## Phylogeny

BUB1B (BubR1) and BUB1 originated from an ancestral spindle-checkpoint kinase that duplicated early in eukaryotic evolution, creating the Bub1/BubR1 sub-family within the CMGC group of the protein-kinase–like (PKL) superfamily first catalogued by the Manning kinome (bolanosgarcia2011bub1andbubr1 pages 8-9).  
Orthologs are conserved from yeast Mad3 (Saccharomyces cerevisiae, Schizosaccharomyces pombe) and Drosophila melanogaster BubR1 to vertebrates such as Xenopus laevis, Mus musculus and Homo sapiens, underscoring a deeply conserved spindle-checkpoint role (elowe2011bub1andbubr1 pages 5-6, chen2002bubr1isessential pages 1-2).  
Despite retaining the bilobal Bub1-like fold, the BubR1 C-terminal lobe contains degenerate HRD and DFG motifs, rationalising its classification as a pseudokinase (breit2015roleofintrinsic pages 13-14, bolanosgarcia2011bub1andbubr1 pages 4-5).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇌ ADP + [protein]-O-phospho-Ser/Thr (canonical Ser/Thr kinase reaction)  
Purified BubR1 binds ATP but shows no detectable phosphoryl-transfer, confirming catalytic silence (breit2015roleofintrinsic pages 13-14).

## Cofactor Requirements

ATP binding is magnesium-independent in vitro and no divalent-cation requirement has been demonstrated (breit2015roleofintrinsic pages 2-4).

## Substrate Specificity

Large-scale peptide library profiling failed to detect a BubR1 consensus motif, consistent with its pseudokinase status (corno2023abifunctionalkinase–phosphatase pages 22-22, breit2015roleofintrinsic pages 13-14).

## Structure

Domain organisation  
• KEN box 1 (≈ res 7-13): high-affinity CDC20 binder initiating mitotic-checkpoint complex (MCC) assembly (krenn2014insightsintothe pages 30-34).  
• Triple TPR stack (≈ res 40-200): scaffolds MCC interactions (krenn2014insightsintothe pages 30-34).  
• KEN box 2 (≈ res 300-306): blocks APC/C substrate entry (krenn2014insightsintothe pages 30-34).  
• GLEBS motif/TPR helix (≈ res 400-440): wraps around BUB3 for kinetochore targeting; crystal structure reveals a canonical peptide-binding groove (bolanosgarcia2011bub1andbubr1 pages 4-5).  
• KARD/LxxIxE motif (≈ res 665-682): docks PP2A-B56 phosphatase (overlack2015amolecularbasis pages 14-16).  
• C-terminal pseudokinase domain (≈ res 720-1050): retains the bilobal topology but lacks an intact catalytic and regulatory spine (breit2015roleofintrinsic pages 13-14).

Three-dimensional information  
Cryo-EM of the human MCC (PDB 6F0I) positions BubR1 beside BUB3, MAD2 and CDC20 at the APC/C inhibitory interface (banerjee2022bubr1recruitmentto pages 15-15, unknownauthors2014evolutionandregulation pages 95-98).  
The PP2A-B56–BubR1 KARD complex (PDB 4OMA) shows an LxxIxE docking groove on B56 engaging BubR1 (overlack2015amolecularbasis pages 23-24).  
AlphaFold full-length modelling agrees with experimental data and confirms an inactive kinase conformation with a disrupted R-spine (banerjee2022bubr1recruitmentto pages 15-15).

Key catalytic/regulatory features  
• Activation segment is truncated and displaced, abolishing the Lys-Glu catalytic salt bridge (breit2015roleofintrinsic pages 13-14).  
• Hydrophobic spine is broken at HRD and DFG positions, explaining loss of catalysis (bolanosgarcia2011bub1andbubr1 pages 4-5).

## Regulation

Post-translational modifications  
Acetylation  
– Lys250: acetylated by PCAF, stabilising BubR1 during prometaphase (bloom2021physiologicalrelevanceof pages 11-12).  
– Deacetylated by HDAC2/3 and SIRT2; deacetylation permits subsequent SUMOylation and facilitates checkpoint silencing (bloom2021physiologicalrelevanceof pages 15-16).  
– Lys668: acetylated by CBP, marking BubR1 for APC/C-mediated ubiquitination; SIRT2 reverses this, linking protein stability to NAD⁺ levels and ageing (unknownauthors2022investigatingtherelationship pages 13-17).

SUMOylation  
– Lys250 conjugation by SUMO-1 accelerates BubR1 removal from kinetochores, promoting anaphase onset (yang2012sumoylatedbubr1plays pages 1-2).

Phosphorylation  
– Thr680 (CDK1) and Ser676 (Plk1) within the KARD enhance PP2A-B56 binding and stabilise correct kinetochore-microtubule attachments (corno2023abifunctionalkinase–phosphatase pages 22-22, bloom2021physiologicalrelevanceof pages 4-5).  
– Thr620 (CDK1) creates a Plk1-docking phospho-epitope driving further KARD phosphorylation (bloom2021physiologicalrelevanceof pages 13-15).  
– Unattached kinetochores trigger BubR1 hyperphosphorylation in a Bub1/Mad1-dependent manner to amplify SAC signalling (chen2002bubr1isessential pages 1-2).

Ubiquitination  
– APC/C ubiquitinates BubR1 during late mitosis, targeting it for proteasomal degradation and contributing to checkpoint silencing (bloom2021physiologicalrelevanceof pages 9-11).

Allosteric/conformational regulation  
BUB3 binding orders the GLEBS helix and is indispensable for kinetochore localisation and MCC incorporation (overlack2015amolecularbasis pages 12-14).  
PP2A-B56 engagement via the KARD counteracts Aurora-B phosphorylation to stabilise bi-oriented attachments and promotes SAC silencing (overlack2015amolecularbasis pages 14-16).

## Function

Expression  
BubR1 accumulates from late G₂, peaks in mitosis and declines with organismal age, linking reduced levels to cellular senescence (bloom2021physiologicalrelevanceof pages 1-2).

Mitotic checkpoint  
BUB1–BUB3 bound to Mps1-phosphorylated MELT repeats on KNL1 recruits BubR1–BUB3 via loop-mediated dimerisation, nucleating MCC assembly (unknownauthors2014evolutionandregulation pages 13-15, banerjee2022bubr1recruitmentto pages 15-15).  
Within the MCC, BubR1, BUB3, MAD2 and CDC20 inhibit APC/C, preventing securin and cyclin-B ubiquitination until chromosome bi-orientation is achieved (overlack2017bubr1promotesbub3dependent pages 1-2, krenn2014insightsintothe pages 30-34).

Kinetochore–microtubule regulation  
The BubR1 KARD recruits PP2A-B56 to oppose Aurora-B activity and stabilise end-on attachments (overlack2015amolecularbasis pages 14-16).  
Interaction with the kinesin CENP-E links tension sensing to checkpoint robustness (elowe2011bub1andbubr1 pages 2-3).  
Co-operation with APC/EB1 further supports chromosome congression (breit2015roleofintrinsic pages 20-21).

Signalling network  
Upstream regulators: Bub1 kinase, Mps1 kinase, CDK1 and Plk1 (banerjee2022bubr1recruitmentto pages 15-15, bloom2021physiologicalrelevanceof pages 4-5).  
Downstream effect: APC/C inhibition maintains metaphase arrest until proper spindle attachment (krenn2014insightsintothe pages 30-34).

## Other Comments

Disease associations  
Biallelic germline mutations in BUB1B cause mosaic variegated aneuploidy syndrome, characterised by constitutional aneuploidy and childhood cancer predisposition (bloom2021physiologicalrelevanceof pages 16-17, bolanosgarcia2011bub1andbubr1 pages 10-10).  
Somatic over-expression or mutation correlates with chromosomal instability and poor prognosis in gastric, bladder, pancreatic, liver and breast cancers (bolanosgarcia2011bub1andbubr1 pages 9-10).  
Age-related decline of BubR1 protein promotes tissue degeneration and tumour susceptibility in mouse models (bloom2021physiologicalrelevanceof pages 1-2).  
Missense substitutions at Lys250 or within the pseudokinase domain disrupt protein stability or MCC assembly, driving aneuploidy and oncogenesis (bloom2021physiologicalrelevanceof pages 13-15, bolanosgarcia2011bub1andbubr1 pages 5-7).

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