Phylogeny  
• CAMK group → AMPK/SNF1‐related subfamily → MARK branch (marx2006structuralvariationsin pages 1-1)  
• Orthologs: S. cerevisiae KIN1/KIN2, S. pombe kin1, C. elegans PAR-1, D. melanogaster PAR-1, X. laevis XPAR-1A/B, R. norvegicus Mark2, M. musculus Mark2, Homo sapiens MARK1/3/4 (unknownauthors2007regulationofthe pages 7-11)  
• Phylogenomic survey across 94 eukaryotes retains MARK kinases as a conserved LECA-derived clade within CAMK (wijk2020thefirsteukaryotic pages 5-8)  
• Shared domain architecture and sequence homology link MARK2 to other AMPK-family members such as BRSK and SIK (matenia2009thetauof pages 1-2)

Reaction Catalyzed  
ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (panneerselvam2006structureofthe pages 1-2)

Cofactor Requirements  
• Two Mg²⁺ ions coordinate ATP and the catalytic Asp193 for phosphoryl transfer (ahrari2017interconversionofinactive pages 19-21)

Substrate Specificity  
• Preferred consensus: K-X-G-S*/T* motif identified on MAP2/4 and TAU repeats (panneerselvam2006structureofthe pages 1-2)  
• Basophilic, serine-directed profile; Met at DFG + 1 correlates with weaker sequence stringency yet serine preference (sugiyama2019largescalediscoveryof pages 6-8)

Structure  
• Domain layout: N-terminal leader | bilobed catalytic domain (Lys82–Asp199 core) | UBA | proline-rich spacer | C-terminal tail with KA1 (panneerselvam2006structureofthe pages 1-2)  
• Experimental structures: human catalytic-UBA 1Y8G (2.6 Å); additional MARK2 entries 1ZMU/1ZMV/1ZMW; rat MARK2 model 2WZJ (panneerselvam2006structureofthe pages 11-11, jenardhanan2014thestructuralanalysis pages 23-25)  
• Active state: pThr208 orders the activation loop, completes Lys82–Glu100 salt bridge and regulatory spine assembly (ahrari2017interconversionofinactive pages 19-21)  
• Inactive state: αC-out, wide catalytic cleft, partially disordered loop; UBA clamps N-lobe restricting inter-lobe motion (panneerselvam2006structureofthe pages 8-9)  
• UBA autoinhibition reduces responsiveness to T208 phosphorylation (unknownauthors2006structuralvariationsin pages 10-13)  
• Unique structural element: β9 strand Asn198-Glu199 forms an atypical RD pocket; DFG remains Asp-in in both states (ahrari2017interconversionofinactive pages 19-21)

Regulation  
Phosphorylation  
– Thr208: activating, by LKB1 or MARKK/TAO-1 (panneerselvam2006structureofthe pages 1-2)  
– Ser212: inhibitory, by GSK3β (timm2008structureandregulation pages 4-5)  
– Ser409: inhibitory, by PKA (deng2015proteinkinasea pages 8-10)  
– Ser400: inhibitory, by PKD (deng2015proteinkinasea pages 8-10)  
– Thr595: inhibitory, by aPKC; creates 14-3-3 docking site (deng2015proteinkinasea pages 8-10)  
– Ser92 & Thr294: modulatory, by CaMKI (deng2015proteinkinasea pages 8-10)

Ubiquitination  
• E3 ligases TRAF2 and Smurf1 tag MARK2 for proteasomal degradation (deng2015proteinkinasea pages 8-10)

Protein/Domain interactions  
• 14-3-3 binds pThr595 or pSer409, sequestering and inhibiting the kinase (deng2015proteinkinasea pages 8-10, timm2008structureandregulation pages 4-5)  
• PAK5 associates with the catalytic domain and suppresses activity (timm2008structureandregulation pages 4-5)

Function  
• Phosphorylates MAPT/TAU, MAP2 and MAP4 at KXGS sites, detaching them from microtubules and promoting turnover (panneerselvam2006structureofthe pages 1-2)  
• Controls neuronal polarity, axon specification and neurite extension (timm2008structureandregulation pages 4-5)  
• Regulates epithelial polarity via phosphorylation of RAB11FIP2 (panneerselvam2006structureofthe pages 1-2)  
• Upstream activators: LKB1-STRAD-MO25 complex and MARKK/TAO-1 (panneerselvam2006structureofthe pages 1-2)  
• Downstream effects include modulation of WNT/β-catenin signalling; loss-of-function variants suppress pathway activity in neural progenitors (gong2024mark2variantscause pages 3-4)  
• PKA-mediated Ser409 phosphorylation counteracts MARK2-induced microtubule destabilization in neurons (deng2015proteinkinasea pages 8-10)

Inhibitors  
• 9-oxo-9H-acridin-10-yl derivatives (e.g., 30019, 30195, 30197, 30199) occupy the ATP hinge (Tyr131) and show favourable binding free energy in MARK2 models (jenardhanan2014thestructuralanalysis pages 13-15, jenardhanan2014thestructuralanalysis pages 21-23)  
• Broad-spectrum ATP-competitive compounds OTSSP167 and AZ13599185 reported to inhibit MARK family kinases (annadurai2017microtubuleaffinityregulatingkinases pages 11-11)

Other Comments  
• Hyperphosphorylation of TAU by MARK2 contributes to Alzheimer-type neurofibrillary pathology (panneerselvam2006structureofthe pages 1-2, timm2008structureandregulation pages 4-5)  
• Pathogenic missense variants p.A80V, p.G135R, p.F194S, p.R302Q (kinase domain) and p.V752A, p.R764P (KA1) destabilize the protein and are linked to autism spectrum disorder, intellectual disability and speech impairment (gong2024mark2variantscause pages 8-9)

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