## Phylogeny

CDC42BPG encodes myotonic-dystrophy-kinase-related, CDC42-binding kinase γ (MRCK γ), a member of the AGC kinase group within the ROCK/DMPK/MRCK branch of Rho-GTPase-regulated kinases (Unbekandt & Olson, 2014).  
The catalytic domain shares ~44 % identity with MRCK β and ~60 % with dystrophia-myotonica protein kinase (DMPK) (Zhao & Manser, 2015; Unbekandt & Olson, 2014).  
Verified orthologs exist in mouse (Cdc42bpg), rat (Cdc42bpg), zebrafish (cdc42bpg), Xenopus (cdc42bpg), Drosophila (Genghis-Khan/Gek) and Caenorhabditis elegans MRCK homologs (Unbekandt & Olson, 2014; Zhao & Manser, 2015).

## Reaction Catalyzed

Protein-L-Ser/Thr + ATP ⇄ Protein-L-Ser/Thr-phosphate + ADP (Leung et al., 1998).

## Cofactor Requirements

Mg²⁺ is required for catalytic turnover (Zhao & Manser, 2015).

## Substrate Specificity

• Prefers acidic residues at −3/−2 and a hydrophobic residue at +1 relative to the phosphorylation site (Ruscetta et al., 2023).  
• Verified phosphosites: MLC2 Ser19 and Thr18; MYPT1 Thr696, Thr853 and Ser472; activation-loop sites of LIMK1/2; moesin/ERM proteins (Unbekandt & Olson, 2014; Zhao & Manser, 2015).

## Structure

Linear organisation: N-terminal kinase domain – C1 zinc-finger – PH-like segment – extended coiled-coil/Citron-homology region with an autoinhibitory kinase-inhibitory motif (KIM) – C-terminal CRIB domain that binds CDC42/TC10 (Unbekandt & Olson, 2014; Zhao & Manser, 2015).  
The crystal structure of MRCK β (PDB 3TKU) reveals an active kinase fold with an ordered activation loop and dimeric interface; this architecture is conserved in MRCK γ (Zhao & Manser, 2015).  
An AlphaFold model for full-length MRCK γ (AF-Q6DT37-F1) shows canonical HRD and DFG motifs, an intact regulatory αC-helix and a continuous hydrophobic spine (Ruscetta et al., 2023).  
The catalytic lysine equivalent to Lys105 in MRCK β is essential for ATP binding (Unbekandt et al., 2020).  
Full-length MRCK assembles mainly as inactive tetramers (~900 kDa) that dissociate upon activation (Zhao & Manser, 2015).

## Regulation

• Binding of GTP-loaded CDC42 or TC10 to the CRIB domain relieves KIM-mediated autoinhibition and targets the kinase to cortical actin (Zhao & Manser, 2015).  
• Diacylglycerol or phorbol esters engage the C1 domain and enhance activity ~3-fold (Zhao & Manser, 2015).  
• Inter- and intramolecular coiled-coil contacts generate an autoinhibited state; N-terminal dimerisation and trans-autophosphorylation overcome this brake (Tan et al., 2001).  
• Family autophosphorylation on Thr1108 (validated in MRCK β) serves as an activity biomarker; the homologous MRCK γ site is unverified (Unbekandt et al., 2020).  
• Phosphorylation-dependent 14-3-3 binding, ubiquitination, and transcriptional control via promoter methylation and Sp1 have been reported (Ruscetta et al., 2023; Zhao & Manser, 2015).

## Function

Highest expression in heart, skeletal muscle, blood, larynx and peripheral nervous system; low or absent in roughly one-third of GTEx tissues (Unbekandt & Olson, 2014; Ruscetta et al., 2023).  
Upstream regulators: CDC42-GTP, TC10-GTP, diacylglycerol/phorbol esters (Zhao & Manser, 2015).  
Interacting partners: LRAP35a, LRAP25, MYO18A and LIMK1 (Zhao & Manser, 2015; Ruscetta et al., 2023).  
Downstream events: phosphorylation of MLC2 and inhibitory phosphorylation of MYPT1 increase local actomyosin contractility, while LIMK activation stabilises F-actin, promoting lamellipodial dynamics and invasive migration (Zhao & Manser, 2015; Unbekandt & Olson, 2014).

## Inhibitors

• BDP5290 (TCPA-1): ATP-competitive, >50-fold selectivity over ROCK; blocks tumour-cell invasion (Zhao & Manser, 2015; Unbekandt et al., 2014).  
• BDP9066 and C21: second-generation, high-potency, MRCK-selective inhibitors (Unbekandt & Olson, 2014; Ruscetta et al., 2023).  
• Chelerythrine, staurosporine, fasudil and Y-27632 inhibit MRCK but lack isoform selectivity (Unbekandt & Olson, 2014).

## Other Comments

CDC42BPG amplification or over-expression is reported in ovarian, breast, oral, pancreatic and oesophageal cancers and correlates with aggressive phenotypes (Unbekandt & Olson, 2014; Ruscetta et al., 2023).  
Selective MRCK inhibition suppresses invasion in RAS-driven squamous-cell carcinoma, breast-cancer and glioma models (Unbekandt et al., 2014; Unbekandt et al., 2020).  
Gene location: chromosome 11q13.1 (Ruscetta et al., 2023).

## 9. References

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