## Phylogeny

CDC42BPG encodes MRCK γ, a member of the AGC kinase group within the ROCK/DMPK/MRCK branch of Rho-GTPase-regulated kinases (unbekandt2014theactinmyosinregulatory pages 1-2).  
The catalytic domain shares ~44 % identity with MRCK β and ~60 % identity with dystrophia-myotonica protein kinase (DMPK) (zhao2015myotonicdystrophykinaserelated pages 1-2, unbekandt2014theactinmyosinregulatory pages 2-4).  
Verified orthologs include Mus musculus Cdc42bpg, Rattus norvegicus Cdc42bpg, Danio rerio cdc42bpg, Xenopus laevis cdc42bpg, Drosophila melanogaster Genghis-Khan (Gek) and Caenorhabditis elegans MRCK homologs (unbekandt2014theactinmyosinregulatory pages 1-2, zhao2015myotonicdystrophykinaserelated pages 5-6).

## Reaction Catalyzed

Protein-L-Ser/Thr + ATP ⇌ Protein-L-Ser/Thr-phosphate + ADP (leung1998myotonicdystrophykinaserelated pages 1-2).

## Cofactor Requirements

Catalytic turnover requires Mg²⁺ (zhao2015myotonicdystrophykinaserelated pages 1-2).

## Substrate Specificity

Sequence-profiling indicates preference for acidic residues at −3 and −2 and a hydrophobic residue at +1 relative to the phospho-acceptor site (ruscetta2023opportunitiesandchallenges pages 2-6).  
Validated phosphosites include: MLC2 Ser19 (mono-phosphorylation) and Thr18 (zhao2015myotonicdystrophykinaserelated pages 4-5); MYPT1 Thr696/Thr853/Ser472 (zhao2015myotonicdystrophykinaserelated pages 4-5); LIMK1/2 activation-loop sites and moesin family ERM proteins (unbekandt2014theactinmyosinregulatory pages 4-6).

## Structure

Domain organisation: N-terminal kinase domain – C1 zinc-finger – PH-like segment – extended coiled-coil/Citron-homology region containing an autoinhibitory kinase-inhibitory motif (KIM) – C-terminal CRIB motif that binds CDC42/TC10 (unbekandt2014theactinmyosinregulatory pages 2-4, zhao2015myotonicdystrophykinaserelated pages 3-4).  
Crystal structure of the paralogue MRCK β (PDB 3TKU) shows an active kinase fold with ordered activation loop and dimeric interface; this architecture is conserved in MRCK γ (zhao2015myotonicdystrophykinaserelated pages 4-5).  
An AlphaFold model is available for full-length MRCK γ (AF-Q6DT37-F1) and displays canonical HRD and DFG motifs, an intact regulatory αC-helix and a continuous hydrophobic spine (ruscetta2023opportunitiesandchallenges pages 1-2).  
The catalytic lysine equivalent to Lys105 in MRCK β is essential for ATP coordination (unbekandt2020thecdc42effector pages 1-3).  
Full-length MRCK forms predominantly inactive tetramers (~900 kDa) that dissociate upon activation (zhao2015myotonicdystrophykinaserelated pages 4-5).

## Regulation

• Binding of GTP-loaded CDC42 or TC10 to the CRIB domain relieves KIM-mediated autoinhibition and recruits the kinase to cortical actin structures (zhao2015myotonicdystrophykinaserelated pages 3-4).  
• Diacylglycerol or phorbol esters engage the C1 domain, producing ~3-fold catalytic enhancement (zhao2015myotonicdystrophykinaserelated pages 3-4).  
• Inter- and intramolecular coiled-coil contacts generate an autoinhibited state; disruption by N-terminal dimerisation and trans-autophosphorylation activates the enzyme (tan2001intermolecularandintramolecular pages 1-2).  
• Family autophosphorylation on Thr1108 (validated in MRCK β) serves as an activity biomarker; the homologous MRCK γ residue remains unverified (unbekandt2020thecdc42effector pages 1-3).  
• Phosphorylation-dependent 14-3-3 binding and ubiquitination have been reported but require further validation (ruscetta2023opportunitiesandchallenges pages 1-2).  
• Gene transcription is regulated by promoter DNA methylation and Sp1 binding (zhao2015myotonicdystrophykinaserelated pages 6-7).

## Function

Expression is highest in heart, skeletal muscle, blood, larynx and peripheral nervous system, with low or absent transcripts in approximately one-third of GTEx tissues (unbekandt2014theactinmyosinregulatory pages 2-4, ruscetta2023opportunitiesandchallenges pages 6-9).  
Upstream regulators: CDC42-GTP, TC10-GTP, diacylglycerol/phorbol esters (zhao2015myotonicdystrophykinaserelated pages 3-4).  
Interacting partners: LRAP35a, LRAP25, MYO18A and LIMK1 assemble signalling complexes at the cell edge (zhao2015myotonicdystrophykinaserelated pages 4-5, ruscetta2023opportunitiesandchallenges pages 2-6).  
Downstream events: phosphorylation of MLC2 and inhibitory phosphorylation of MYPT1 elevate local actomyosin contractility; concomitant LIMK activation stabilises F-actin, facilitating lamellipodial dynamics and invasive migration (zhao2015myotonicdystrophykinaserelated pages 4-5, unbekandt2014theactinmyosinregulatory pages 4-6).

## Inhibitors

BDP5290 (TCPA-1): ATP-competitive; >50-fold selectivity over ROCK; blocks tumour-cell invasion (zhao2015myotonicdystrophykinaserelated pages 4-5, unbekandt2014anovelsmallmolecule pages 1-2).  
BDP9066 and C21: second-generation inhibitors with high potency and maintained MRCK selectivity (unbekandt2014theactinmyosinregulatory pages 7-8, ruscetta2023opportunitiesandchallenges pages 14-16).  
Chelerythrine, staurosporine, fasudil and Y-27632 inhibit MRCK but lack isoform selectivity (unbekandt2014theactinmyosinregulatory pages 4-6).

## Other Comments

Genomic alterations or over-expression of CDC42BPG are observed in ovarian, breast, oral, pancreatic and oesophageal cancers and correlate with aggressive phenotypes (unbekandt2014theactinmyosinregulatory pages 6-7, ruscetta2023opportunitiesandchallenges pages 6-9).  
Selective MRCK inhibition suppresses invasion in RAS-driven squamous-cell carcinoma, breast-cancer and glioma models (unbekandt2014anovelsmallmolecule pages 1-2, unbekandt2020thecdc42effector pages 1-3).  
The gene is located at chromosome 11q13.1 (ruscetta2023opportunitiesandchallenges pages 2-6).

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