## Phylogeny

LRRK2 belongs to the ROCO family of dual‐enzyme proteins and, together with its paralog LRRK1, forms a small branch within the receptor-interacting protein kinase (RIPK) arm of the human kinome (greggio2009leucinerichrepeatkinase pages 3-4).  
Orthologs are conserved across vertebrates (mouse, rat, zebrafish, Xenopus), invertebrates (Caenorhabditis elegans, Drosophila melanogaster) and basal metazoans such as Nematostella vectensis, indicating origin prior to the protostome–deuterostome split (langston2016thefunctionof pages 1-3, marin2006theparkinsondisease pages 8-9).  
ROCO proteins are also present in slime molds, certain plants, bacteria and archaea, demonstrating an ancient but patchy evolutionary distribution (marin2006theparkinsondisease pages 8-9).

## Reaction Catalyzed

Protein-L-Ser/Thr + ATP → Protein-L-phospho-Ser/Thr + ADP (nichols2017lrrk2phosphorylation pages 81-83).

## Cofactor Requirements

Full kinase activity requires GTP binding to the ROC GTPase domain; no divalent metal preference is reported in the cited literature (nichols2017lrrk2phosphorylation pages 81-83).

## Substrate Specificity

LRRK2 phosphorylates a conserved Thr/Ser within the switch-II effector-binding loop of multiple Rab GTPases; the minimal motif is D/N-x-T/S-I/L, exemplified by Rab8A-Thr72 and Rab10-Thr73 (alessi2018lrrk2kinasein pages 1-3, ordonez2019rab8rab10and pages 31-32).  
Confirmed cellular substrates include Rab3A/B/C/D, Rab5A/B/C, Rab8A/B, Rab10, Rab12, Rab29, Rab35 and Rab43 (alessi2018lrrk2kinasein pages 3-5).  
Moesin and other ERM family members are additional serine/threonine targets linked to cytoskeletal regulation (nichols2017lrrk2phosphorylation pages 81-83).

## Structure

Domain layout: N-terminal armadillo/ankyrin repeats – leucine-rich repeats – ROC GTPase – COR linker – Ser/Thr kinase – WD40 repeat (greggio2009leucinerichrepeatkinase pages 3-4).  
Cryo-EM structures of full-length human LRRK2 in complex with Rab29 (EMD-26034; PDB 7LI3) reveal monomeric, dimeric and tetrameric assemblies; activation requires COR–kinase hinge rotation and oligomerisation on membranes (zhu2022structuralbasisof pages 14-18).  
Independent cryo-EM analyses resolved inactive and active conformers (PDB 6VP6, 6VRA) highlighting the DFGψ-out/in transition and microtubule-binding interfaces (tasegian2021impactoftype pages 18-18).  
Key catalytic residues: Lys1906 (VAIK), Glu1920 (α-helix-C), Asp2017 (HRD) (zhu2022structuralbasisof pages 14-18).  
The ATP pocket contains two invariant tyrosines in the regulatory and catalytic spines, conferring unusual flexibility and permitting mutant-selective inhibitor design (liu2014uniquefunctionaland pages 10-11).  
Negative-stain and cryo-EM confirm constitutive homodimerisation mediated by COR and WD40 surfaces, essential for maximal activity (sejwal2017cryoemanalysisof pages 11-11).

## Regulation

Post-translational phosphorylation  
• Autophosphorylation at Ser1292 tracks intrinsic kinase activity and is elevated by pathogenic mutations (tasegian2021impactoftype pages 1-2).  
• CK1α and PKA phosphorylate Ser910, Ser935, Ser955 and Ser973, creating 14-3-3 docking sites; kinase inhibition or PD-linked mutations trigger dephosphorylation, 14-3-3 release and microtubule relocalisation (nichols2017lrrk2phosphorylation pages 81-83, tasegian2021impactoftype pages 1-2).

Allosteric control  
• GTP-loaded ROC domain favours the active kinase conformation; ROC mutants such as R1441C diminish GTP hydrolysis, thereby elevating kinase output (nichols2017lrrk2phosphorylation pages 81-83).  
• Rab29 binding to the ARM domain drives membrane recruitment, higher-order oligomerisation and kinase activation (zhu2022structuralbasisof pages 14-18).

## Function

Expression profile  
High expression in peripheral immune cells (monocytes, macrophages, neutrophils), kidney, lung and selected neuronal populations (alessi2018lrrk2kinasein pages 1-3, liu2014uniquefunctionaland pages 15-16, tasegian2021impactoftype pages 18-19).

Cellular and pathway roles  
• Regulates endolysosomal trafficking, autophagy-lysosome dynamics and primary cilium maintenance through broad Rab phosphorylation (alessi2018lrrk2kinasein pages 3-5, ordonez2019rab8rab10and pages 31-32).  
• Maintains centrosomal cohesion and ciliogenesis via Rab8/Rab10 signalling and RILPL1 interaction (ordonez2019rab8rab10and pages 32-33).  
• Modulates NLRC4 inflammasome activation and pro-inflammatory cytokine production in innate immune cells (alessi2018lrrk2kinasein pages 1-3).  
• Alters neurite morphology and enhances α-synuclein toxicity when hyperactive (liu2014uniquefunctionaland pages 15-16).  
• Drosophila LRRK controls lysosomal positioning through Rab7, illustrating conserved endolysosomal regulation (dodson2012rolesofthe pages 1-1).

## Inhibitors

Type I ATP-competitive inhibitors  
• GSK2578215A and MLi-2 are potent, brain-penetrant probes that induce Ser935 dephosphorylation and have progressed to human studies (alessi2018lrrk2kinasein pages 3-5, tasegian2021impactoftype pages 16-18).  
• PF-06447475 and LRRK2-IN-1 offer selective cellular inhibition with robust biomarker engagement (tasegian2021impactoftype pages 18-18).

Type II inhibitors  
• GZD-824, Rebastinib and Ponatinib bind the open, inactive DFGψ-out state, suppress Rab phosphorylation without affecting biomarker Ser935, but currently lack selectivity (tasegian2021impactoftype pages 16-18).

Mutant-selective chemistry  
• The atypical ATP pocket enables development of mutant-selective inhibitors such as SRI-29132, exploiting the hydrophobic spine flexibility (liu2014uniquefunctionaland pages 1-1).

## Other Comments

Missense variants G2019S (kinase domain) and R1441C/G/H (ROC domain) increase kinase activity two- to four-fold and are the most common genetic causes of autosomal-dominant Parkinson’s disease (alessi2018lrrk2kinasein pages 1-3, liu2014uniquefunctionaland pages 1-1).  
Systemic LRRK2 inhibition in rodents and non-human primates produces reversible lung and kidney alterations attributable to suppressed autophagy-lysosome function, highlighting on-target safety liabilities (alessi2018lrrk2kinasein pages 3-5, tasegian2021impactoftype pages 16-18).

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