## Phylogeny

Leucine-rich repeat kinase 1 (LRRK1) is a ROCO family member placed within the Tyrosine-Kinase-Like (TKL) group of the human kinome (gilsbach2014structuralbiologyof pages 1-2).  
Vertebrate LRRK1 and LRRK2 arose from duplication of a single ancestral LRRK gene; invertebrates such as Caenorhabditis elegans (LRK-1) and Drosophila melanogaster (dLRRK) possess a single ortholog (mata2006lrrk2inparkinsons pages 2-3).  
Additional orthologs occur in Dictyostelium discoideum (Roco4) and Chlorobium tepidum, underscoring conservation of the ROC-COR-kinase cassette (gilsbach2014structuralbiologyof pages 2-4).  
Human LRRK1 shares ~70 % sequence identity with LRRK2 across the ROC, COR and kinase domains (mata2006lrrk2inparkinsons pages 3-4).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (malik2021decipheringthelrrk pages 8-10).

## Cofactor Requirements

Catalytic activity requires Mg²⁺, supplied as MgATP in all in-vitro kinase assays (malik2021decipheringthelrrk pages 8-10).  
Dependence on Mn²⁺ is not reported.

## Substrate Specificity

• High-affinity substrate Rab7A; LRRK1 phosphorylates Ser72 within the switch-II effector motif (malik2021decipheringthelrrk pages 1-2).  
• Rab8A and Rab10 are not phosphorylated by LRRK1, indicating narrow Rab selectivity (malik2021decipheringthelrrk pages 1-2).  
• OSTM1 is phosphorylated at Thr328 / Ser329 in osteoclasts, stabilising the protein (shen2023leucinerepeatrich pages 8-11).  
• CLIP-170 is phosphorylated in HEK293 cells; the modification site is unmapped (xing2017roleandmechanism pages 5-6).  
• A global consensus motif beyond the Rab switch-II context has not been defined (malik2021decipheringthelrrk pages 17-20).

## Structure

Full-length human LRRK1 (2 015 aa) forms an antiparallel homodimer with a central ROC-COR-kinase core and peripheral ANK/LRR repeats as visualised by 25 Å cryo-EM (sejwal2017cryoemanalysisof pages 5-8).  
Domain organisation comprises N-terminal ANK repeats, an LRR domain, a ROC GTPase domain containing canonical G1–G5 motifs, adjacent CORA and CORB subdomains, a serine/threonine kinase domain bearing VAIK, HRD and DFG catalytic motifs, and a C-terminal WD40 β-propeller (gilsbach2014structuralbiologyof pages 4-6, xing2017roleandmechanism pages 5-6).  
The WD40 domain is supported by sequence and functional data yet was not resolved in the low-resolution EM map, creating a structural discrepancy (sejwal2017cryoemanalysisof pages 1-2, zhang2023lrrk2structurebasedactivation pages 10-12).  
Within CORB, residues Ser1064, Ser1074 and Thr1075 lie in a flexible loop adjacent to the kinase αC-helix and constitute a phosphorylation-controlled allosteric switch (malik2022pkcisoformsactivate pages 1-2).  
ROC Lys651 is required for GTP binding; the K651A mutation abolishes nucleotide binding and kinase output (xing2017roleandmechanism pages 5-6).  
No high-resolution crystal structure is available; AlphaFold modelling predicts a canonical bilobal kinase fold consistent with experimental data (gilsbach2014structuralbiologyof pages 4-6).

## Regulation

Post-translational modifications  
– PKCα, PKCβ and PKCθ phosphorylate Ser1064, Ser1074 and Thr1075; Thr1075 is indispensable for activation, and a triple phosphomimetic increases basal activity three-fold (malik2022pkcisoformsactivate pages 8-10).  
– Phorbol ester or EGF stimulation enhances Rab7A Ser72 phosphorylation via PKC-dependent LRRK1 activation (malik2021decipheringthelrrk pages 17-20).  
– LRRK1 autophosphorylates in vitro; phosphorylation is absent in the kinase-dead D1409A mutant (malik2021decipheringthelrrk pages 8-10).  
– PPM1H selectively dephosphorylates Rab7A Ser72 (malik2021decipheringthelrrk pages 1-2).

Conformational and allosteric control  
– Homodimerisation through the ROC-COR scaffold is visualised by cryo-EM and is required for full catalytic activity (sejwal2017cryoemanalysisof pages 5-8).  
– Truncation of the WD40 domain disrupts dimer formation and abolishes kinase function (xing2017roleandmechanism pages 5-6).

## Function

Expression  
LRRK1 is expressed in bone, liver, lung and brain, with marked up-regulation during late osteoclast differentiation (xing2017roleandmechanism pages 3-5, xing2017roleandmechanism pages 5-6).

Physiological roles  
– Acts as a negative regulator of bone mass; Lrrk1-null mice display severe metaphyseal osteopetrosis and the highest trabecular bone mass among >4 500 knockout strains (shen2023leucinerepeatrich pages 11-12).  
– Phosphorylates and stabilises OSTM1, enabling peripheral localisation of secretory lysosomes and efficient bone resorption by osteoclasts (shen2023leucinerepeatrich pages 8-11).  
– Rab7A Ser72 phosphorylation enhances Rab7A–RILP binding and centripetal trafficking of EGF-containing endosomes (xu2021theregulationof pages 11-12).

Interactors and pathways  
Confirmed interactors include Rab7A, APPL1 and Hsc70, linking LRRK1 to vesicle-trafficking modules (xing2017roleandmechanism pages 7-9).  
PKC isoforms function as direct upstream activators (malik2022pkcisoformsactivate pages 1-2).

## Inhibitors

The multi-target kinase inhibitor GZD-824 inhibits both LRRK1 and LRRK2, whereas LRRK2-selective compounds do not affect LRRK1 (malik2021decipheringthelrrk pages 1-2).

## Other Comments

Homozygous loss-of-function mutations in human LRRK1 cause autosomal-recessive osteosclerotic metaphyseal dysplasia, closely mirroring the osteopetrotic phenotype of Lrrk1-null mice (xing2017roleandmechanism pages 3-5).  
LRRK1 is not implicated in Parkinson’s disease, underscoring functional divergence from its paralog LRRK2 (xing2017roleandmechanism pages 5-6).  
The presence of a WD40 domain remains disputed, with sequence analyses supporting its existence and cryo-EM unable to resolve it at current resolution (sejwal2017cryoemanalysisof pages 1-2, zhang2023lrrk2structurebasedactivation pages 10-12).

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