## Phylogeny

Leucine-rich repeat kinase 1 (LRRK1) belongs to the ROCO family within the Tyrosine-Kinase-Like (TKL) branch of the human kinome (Gilsbach & Kortholt, 2014). Vertebrate LRRK1 and LRRK2 arose from a duplication of a single ancestral gene, whereas invertebrates such as Caenorhabditis elegans (LRK-1) and Drosophila melanogaster (dLRRK) retain only one orthologue (Mata et al., 2006). Additional homologues are present in Dictyostelium discoideum (Roco4) and Chlorobium tepidum, highlighting conservation of the ROC–COR–kinase cassette (Gilsbach & Kortholt, 2014). Human LRRK1 shares ~70 % sequence identity with LRRK2 across the ROC, COR and kinase domains (Mata et al., 2006).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇄ ADP + [protein]-O-phospho-Ser/Thr (Malik et al., 2021).

## Cofactor Requirements

Mg²⁺ is essential; activity is assayed with MgATP. Mn²⁺ dependence has not been reported (Malik et al., 2021).

## Substrate Specificity

• High-affinity substrate Rab7A, phosphorylated at Ser72 within the switch-II motif (Malik et al., 2021).  
• Rab8A and Rab10 are not substrates, indicating narrow Rab selectivity (Malik et al., 2021).  
• OSTM1 is phosphorylated at Thr328/Ser329 in osteoclasts, stabilising the protein (Shen et al., 2023).  
• CLIP-170 is phosphorylated in HEK293 cells; site not mapped (Xing et al., 2017).  
• A global consensus motif beyond the Rab switch-II context has not been defined (Malik et al., 2021).

## Structure

Full-length human LRRK1 (2 015 aa) forms an antiparallel homodimer featuring an N-terminal ANK repeat region, an LRR domain, a ROC GTPase (G1–G5 motifs), CORA and CORB subdomains, a serine/threonine kinase domain (VAIK, HRD, DFG motifs) and a C-terminal WD40 β-propeller (Gilsbach & Kortholt, 2014; Sejwal et al., 2017; Xing et al., 2017). Cryo-EM (25 Å) visualises the dimeric ROC-COR-kinase core but could not resolve the WD40 domain (Sejwal et al., 2017). Within CORB, Ser1064, Ser1074 and Thr1075 constitute a phosphorylation-controlled allosteric loop adjacent to the kinase αC-helix (Malik et al., 2022). ROC Lys651 is essential for GTP binding; K651A abolishes nucleotide binding and kinase activity (Xing et al., 2017). No high-resolution crystal structure is available, but AlphaFold predicts a canonical bilobal kinase fold consistent with experimental data (Gilsbach & Kortholt, 2014).

## Regulation

Post-translational modifications  
– PKCα, PKCβ and PKCθ phosphorylate Ser1064, Ser1074 and Thr1075; Thr1075 is critical for activation, and a triple phosphomimetic boosts basal activity ~3-fold (Malik et al., 2022).  
– Phorbol ester or EGF stimulation enhances Rab7A Ser72 phosphorylation via PKC-dependent activation of LRRK1 (Malik et al., 2021).  
– LRRK1 autophosphorylates in vitro; phosphorylation is absent in the kinase-dead D1409A variant (Malik et al., 2021).  
– PPM1H selectively dephosphorylates Rab7A Ser72 (Malik et al., 2021).

Conformational/allosteric control  
– Homodimerisation through the ROC-COR scaffold is required for full activity (Sejwal et al., 2017).  
– WD40 truncation disrupts dimerisation and abolishes kinase function (Xing et al., 2017).

## Function

Expression  
Detected in bone, liver, lung and brain, with marked up-regulation during late osteoclast differentiation (Xing et al., 2017).

Physiological roles  
– Negative regulator of bone mass; Lrrk1-null mice exhibit severe metaphyseal osteopetrosis (Shen et al., 2023).  
– Phosphorylates/stabilises OSTM1, promoting lysosomal trafficking required for bone resorption (Shen et al., 2023).  
– Rab7A Ser72 phosphorylation enhances Rab7A–RILP binding and centripetal trafficking of EGF-containing endosomes (Xu et al., 2021).

Interactors and pathways  
Confirmed interactors: Rab7A, APPL1, Hsc70 (Xing et al., 2017).  
Upstream activators: PKC isoforms (Malik et al., 2022).

## Inhibitors

The multi-target kinase inhibitor GZD-824 blocks both LRRK1 and LRRK2, whereas LRRK2-selective compounds do not inhibit LRRK1 (Malik et al., 2021).

## Other Comments

Homozygous loss-of-function mutations in LRRK1 cause autosomal-recessive osteosclerotic metaphyseal dysplasia, paralleling the Lrrk1-null mouse phenotype (Xing et al., 2017). LRRK1 is not implicated in Parkinson’s disease, underscoring functional divergence from LRRK2 (Xing et al., 2017). The existence of a WD40 domain is supported by sequence analysis but remains unresolved structurally (Sejwal et al., 2017; Zhang & Kortholt, 2023).

## References

Gilsbach, B. K., & Kortholt, A. (2014). Structural biology of the LRRK2 GTPase and kinase domains: implications for regulation. Frontiers in Molecular Neuroscience, 7, 32. https://doi.org/10.3389/fnmol.2014.00032

Malik, A. U., Karapetsas, A., Nirujogi, R. S., Mathea, S., Pal, P., Lis, P., Taylor, M., Purlyte, E., Gourlay, R., Dorward, M., Weidlich, S., Toth, R., Polinski, N., Knapp, S., Tonelli, F., & Alessi, D. (2021). Deciphering the LRRK code: LRRK1 and LRRK2 phosphorylate distinct Rab proteins and are regulated by diverse mechanisms. Biochemical Journal, 478, 553–578. https://doi.org/10.1042/BCJ20200937

Malik, A. U., Karapetsas, A., Nirujogi, R. S., Chatterjee, D., Phung, T. K., Wightman, M., Gourlay, R., Morrice, N., Mathea, S., Knapp, S., & Alessi, D. R. (2022). PKC isoforms activate LRRK1 kinase by phosphorylating conserved residues (Ser1064, Ser1074 and Thr1075) within the CORB GTPase domain. Biochemical Journal, 479, 1941–1965. https://doi.org/10.1042/BCJ20220308

Mata, I. F., Wedemeyer, W. J., Farrer, M. J., Taylor, J. P., & Gallo, K. A. (2006). LRRK2 in Parkinson’s disease: protein domains and functional insights. Trends in Neurosciences, 29, 286–293. https://doi.org/10.1016/j.tins.2006.03.006

Sejwal, K., Chami, M., Rémigy, H., Vancraenenbroeck, R., Sibran, W., Sütterlin, R., Baumgartner, P., McLeod, R., Chartier-Harlin, M.-C., Baekelandt, V., Stahlberg, H., & Taymans, J.-M. (2017). Cryo-EM analysis of homodimeric full-length LRRK2 and LRRK1 protein complexes. Scientific Reports, 7, 8667. https://doi.org/10.1038/s41598-017-09126-z

Shen, S., Si, M., Zeng, C., Liu, E. K., Chen, Y., Vacher, J., Zhao, H., Mohan, S., & Xing, W. (2023). Leucine repeat rich kinase 1 controls osteoclast activity by managing lysosomal trafficking and secretion. Biology, 12, 511. https://doi.org/10.3390/biology12040511

Xing, W. R., Goodluck, H., Zeng, C., & Mohan, S. (2017). Role and mechanism of action of leucine-rich repeat kinase 1 in bone. Bone Research, 5, 17003. https://doi.org/10.1038/boneres.2017.3

Xu, L., Nagai, Y., Kajihara, Y., Ito, G., & Tomita, T. (2021). The regulation of Rab GTPases by phosphorylation. Biomolecules, 11, 1340. https://doi.org/10.3390/biom11091340

Zhang, X., & Kortholt, A. (2023). LRRK2 structure-based activation mechanism and pathogenesis. Biomolecules, 13, 612. https://doi.org/10.3390/biom13040612