1. Phylogeny  
   LRRK1, also known as Leucine‐rich repeat serine/threonine‐protein kinase 1 with gene symbol LRRK1 and Uniprot ID Q38SD2, is a member of the ROCO family of proteins characterized by the presence of a Ras‐like GTPase (ROC) domain coupled with a COR (C‐terminal of ROC) domain and a serine/threonine kinase domain (civiero2014geneticstructuraland pages 8-9).  
   Evolutionary analyses reveal that LRRK1 is a vertebrate paralog of LRRK2 and shares a common ancestral origin with other ROCO proteins such as DAPK1 and MASL1, demonstrating a distinct phylogenetic branch within the human kinome (civiero2012biochemicalcharacterizationof pages 13-13).  
   Comparative sequence and domain organization studies have identified orthologs of LRRK1 in diverse mammalian species and suggested that the conserved ROC, COR, and kinase modules were present in the Last Eukaryotic Common Ancestor (greggio2009leucinerichrepeatkinase pages 3-4).  
   Gene duplication events in early vertebrate evolution have given rise to both LRRK1 and LRRK2, with subsequent divergence in regulatory and functional properties while maintaining a similar overall domain architecture (langston2016thefunctionof pages 1-3).  
   Structural conservation of the catalytic domains as well as the accessory interaction modules, such as Ankyrin (ANK) and Leucine Rich Repeats (LRR), further support the grouping of LRRK1 within a core set of eukaryotic kinases that have been maintained throughout evolution (reimer2023structureoflrrk1 pages 1-2).
2. Reaction Catalyzed  
   LRRK1 catalyzes the transfer of a phosphate group from ATP to serine or threonine residues on protein substrates, following the general reaction: ATP + [protein substrate] → ADP + [protein substrate]-phosphate + H⁺ (civiero2012biochemicalcharacterizationof pages 14-14).  
   In particular, LRRK1 phosphorylates Rab proteins that are integral to intracellular trafficking, with Rab7a being a well‐documented substrate (reimer2023structureoflrrk1 pages 10-11).
3. Cofactor Requirements  
   The kinase activity of LRRK1 is dependent on divalent metal cations, with Mg²⁺ serving as the primary cofactor required for optimal ATP binding and phosphotransfer during catalytic activity (civiero2012biochemicalcharacterizationof pages 14-14).
4. Substrate Specificity  
   LRRK1 exhibits substrate specificity consistent with its classification as a serine/threonine kinase by targeting residues within protein substrates that regulate vesicular trafficking (civiero2012biochemicalcharacterizationof pages 14-14).  
   Specifically, experimental studies have demonstrated that Rab7a is phosphorylated by LRRK1, thereby implicating this kinase in the regulation of endocytic processes (reimer2023structureoflrrk1 pages 10-11).
5. Structure  
   LRRK1 displays a multi‐domain architecture that is emblematic of ROCO proteins; its organization comprises an N‐terminal region containing Ankyrin (ANK) repeats and Leucine Rich Repeats (LRR) which mediate protein–protein interactions (reimer2023structureoflrrk1 pages 1-2).  
   Following this interaction module is the central catalytic core that includes the ROC (Ras of Complex proteins) domain responsible for GTP binding and hydrolysis, and the adjacent COR domain that supports dimerization and structural stability (reimer2023structureoflrrk1 pages 1-2).  
   Immediately downstream of the ROC–COR tandem is the serine/threonine kinase domain, which catalyzes the phosphorylation reaction, and this domain is followed by a C‐terminal WD40 domain that is implicated in substrate docking and regulatory interactions (reimer2023structureoflrrk1 pages 1-2).  
   High‐resolution cryo‐electron microscopy and AlphaFold modeling indicate that LRRK1 adopts a J-shaped conformation, wherein the interplay among these domains is arranged to facilitate both autoinhibition and activation (reimer2023structureoflrrk1 pages 1-2).  
   A unique regulatory feature within LRRK1 is the presence of an autoinhibitory loop located in the COR-B portion of the COR domain, which penetrates the kinase active site and helps maintain LRRK1 in an inactive state under basal conditions (reimer2023structureoflrrk1 pages 6-7, reimer2023structureoflrrk1 pages 9-9).  
   Additional structural distinctions include a longer αC helix in the kinase domain compared to its paralog LRRK2, and a differential positioning of the LRR domain that does not occlude the active site, further underscoring divergent regulatory mechanisms between these kinases (reimer2023structureoflrrk1 pages 4-5, reimer2023structureoflrrk1 pages 8-9).
6. Regulation  
   Regulation of LRRK1 activity is achieved through multiple interconnected mechanisms that integrate nucleotide binding and autoinhibitory domain contacts.  
   Binding of GTP to the ROC domain has been shown to stimulate the kinase activity of LRRK1, thereby directly linking its GTPase function to catalytic activation (civiero2012biochemicalcharacterizationof pages 13-13, cookson2015lrrk2pathwaysleading pages 12-13).  
   LRRK1 undergoes homodimerization—a process mediated in part by interactions between the ANK repeats of individual monomers—that is critical for establishing an autoinhibited conformation (reimer2023structureoflrrk1 pages 1-2).  
   A central element in the regulation of LRRK1 is the autoinhibitory COR-B loop, which positions itself within the kinase active site; mutation of a conserved residue, F1065, in this loop has been shown to relieve autoinhibition and consequently enhance kinase activity (reimer2023structureoflrrk1 pages 6-7, reimer2023structureoflrrk1 pages 9-9).  
   Furthermore, phosphorylation events within the COR-B loop region are posited to modulate its conformation, thereby relieving steric inhibition and allowing the kinase activation motif to adopt an active conformation (reimer2023structureoflrrk1 pages 8-9).
7. Function  
   LRRK1 functions as a serine/threonine kinase that plays a significant role in intracellular signaling by phosphorylating Rab GTPases, thereby modulating vesicular trafficking processes (reimer2023structureoflrrk1 pages 10-11).  
   Experimental evidence indicates that the phosphorylation of Rab7a by LRRK1 contributes to the regulation of late endocytic pathways and is a key biochemical event in the control of receptor and vesicle dynamics (reimer2023structureoflrrk1 pages 10-11).  
   Studies further suggest that LRRK1 is involved in endosomal trafficking events, such as the sorting of the epidermal growth factor receptor, which is central to maintaining proper cellular receptor turnover (civiero2014geneticstructuraland pages 8-9).  
   In addition to its role in vesicular trafficking, LRRK1 is proposed, by similarity, to participate in the negative regulation of bone mass through influencing osteoclast maturation; this functional attribution is derived from comparative analyses within the kinase family and sequence homologies (Information section).  
   Proteomic studies have identified interactions between LRRK1 and molecular chaperones, including BAG5 and HSPA8, indicating that LRRK1 is integrated into cellular networks that govern protein quality control and intracellular trafficking (tomkins2020definingtheproximal pages 42-46).
8. Other Comments  
   LRRK1 exhibits lower levels of autophosphorylation when compared to its paralog LRRK2, and it demonstrates limited phosphorylation of substrates that are conventionally modified by LRRK2, reflecting intrinsic differences in catalytic activity between these kinases (civiero2012biochemicalcharacterizationof pages 14-14).  
   Notably, the kinase activity of LRRK1 is stimulated by GTP binding to its ROC domain, an activation mechanism that underscores the coupling between its GTPase and kinase functions (cookson2015lrrk2pathwaysleading pages 12-13).  
   Structural mutagenesis studies have highlighted the critical role of the COR-B loop—in particular, the conserved F1065 residue—in maintaining an autoinhibited state; alterations in this region result in enhanced catalytic activity and provide insight into the molecular determinants of enzyme regulation (reimer2023structureoflrrk1 pages 6-7, reimer2023structureoflrrk1 pages 9-9).  
   Inhibitors that selectively target LRRK1 have not been comprehensively described in the peer-reviewed literature, and clinical modulation of its activity remains an area requiring further investigation (cookson2015lrrk2pathwaysleading pages 12-13).  
   Although LRRK1 has not been directly linked to neurodegenerative disease through genetic mutations, its close structural relationship with LRRK2 and its established role in vesicular trafficking suggest potential relevance in disease pathways that affect intracellular transport processes (langston2016thefunctionof pages 14-16).  
   Additional protein–protein interaction studies have revealed that LRRK1 associates with components of the chaperone network, such as BAG5 and HSPA8, further underscoring its integration into cellular systems responsible for protein quality control and endocytic regulation (tomkins2020definingtheproximal pages 42-46).

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