LRRK2 in Parkinson's disease: protein domains and functional insights

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Parkinson's disease (PD) is the most common motor neurodegenerative disease. Mutations in the gene encoding leucine-rich repeat kinase 2 (*LRRK2*) have been linked recently with autosomal-dominant parkinsonism that is clinically indistinguishable from typical, idiopathic, late-onset PD. Thus, the protein LRRK2 has emerged as a promising therapeutic target for treatment of PD. LRRK2 is extraordinarily large and complex, with multiple enzymatic and protein-interaction domains, each of which is targeted by pathogenic mutations in familial PD. This review places the PD-associated mutations of *LRRK2* in a structural and functional framework, with the ultimate aim of deciphering the molecular basis of LRRK2-associated pathogenesis. This, in turn, should advance our understanding and treatment of familial and idiopathic PD.

Introduction

Parkinson's disease (PD) is a common and cruelly debilitating neurodegenerative disease characterized by tremor, rigidity, bradykinesia and postural instability. Typical of multifactorial diseases, the incidence of PD increases with age, with an estimated 0.3% afflicted at age 50 increasing to 4.3% by age of 85 [1]. PD is incurable and characterized pathologically by the progressive loss of dopaminergic neurons from the substantia nigra pars compacta and the presence of intracellular Lewy bodies in surviving neurons of the brainstem [2]. Although a common unifying cause of PD at the cellular level has not been identified, the culprits might include the formation of cellular aggregates and dysfunction of protein clearance mechanisms, oxidative stress leading to mitochondrial dysfunction and apoptosis, and/or defects in cellular trafficking [3]. There are genetic findings to support each of these theories.

To develop better treatments for PD, it is necessary to identify and therapeutically exploit key molecules involved in the pathogenic process. Mutations in several genes have been genetically linked to PD in recent years [4]. Although these key discoveries in human genetics promise to catalyze our molecular and cellular understanding of PD, mutations in most PD-associated genes have been correlated with early-onset or pathologically atypical forms of the disease. By contrast, the most recently identified PD-associated gene, encoding leucine-rich repeat kinase 2 (LRRK2), has been associated with late-onset PD [5,6]. Because the clinical phenotype ensuing from *LRRK2* mutations resembles idiopathic PD, LRRK2 has emerged as, perhaps, the most relevant player in PD pathogenesis identified to date [7]. Here, we review the state of knowledge with regard to PD-associated amino acid substitutions of LRRK2, placing them in the context of structural domains, and we discuss the potential of LRRK2 as a therapeutic target for the treatment of PD.

LRRK2 – a master regulator gone awry in Parkinson's disease?

Multiple lines of evidence suggest that LRRK2 is key to understanding the etiology of PD. Thus far, at least 20 *LRRK2* mutations (Figure 1, Table 1) have been linked to autosomal-dominant parkinsonism [8–10], accounting for ~7% of familial PD and for a significant fraction of sporadic PD cases [10–12]. The most prevalent LRRK2 amino acid substitution, G2019S, is responsible for ~40% of familial and sporadic PD in Arab samples from North Africa [13,14], ~30% of familial PD in Ashkenazi Jewish populations [15], up to 6% of familial cases in Europe [16–18] and up to 3% of apparently sporadic PD in Europe and North America [11,19]. The predominantly late-onset clinical phenotype associated with this *LRRK2* mutation is largely indistinguishable from idiopathic PD [7], suggesting that a therapeutic strategy directed against LRRK2 G2019S might have broader implications in the treatment of PD. Although few autopsy cases are available, Lewy body pathology (also typical of idiopathic PD) seems most often associated with G2019S [20].

Despite this typical Lewy body pathology, members of a single family bearing the LRRK2 substitution R1441C display pleomorphic pathologies including synucleinopathy, tauopathy or substantia nigral neuronal loss alone [6]. Similarly, the Y1699C substitution has been associated with neuronal loss alone or with nuclear ubiquitin inclusions [21]. The observation of these diverse

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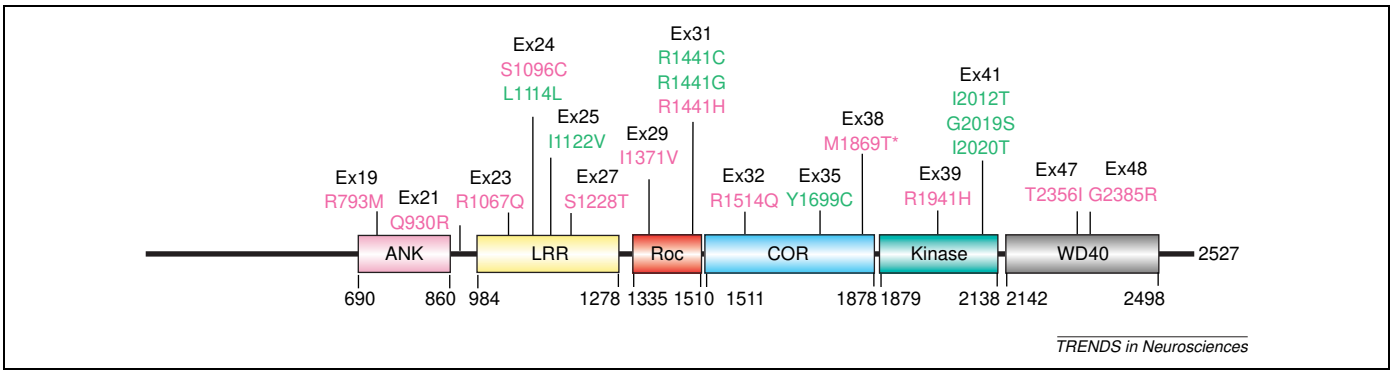

Figure 1. Schematic representation of LRRK2 domain structure. The positions of all putatively pathogenic amino acid substitutions reported to date are highlighted in magenta, whereas amino acid substitutions segregating with disease are shown in green, and the corresponding exon numbers are shown in black. The estimated domain boundaries are indicated by the residue numbers beneath. Abbreviations: ANK, ankyrin repeat region; COR, C terminal of Ras; Ex, exon; LRR, leucine-rich repeat domain; Roc, Ras of complex (GTPase). *M1869 lies within linker region 2 of the COR domain [26].

pathologies strongly suggests that LRRK2 is involved in multiple cellular processes in neurons. The strong dependence of disease penetrance upon age, at least for G2019S, reinforces this idea [17]. Equally intriguing is that PD-associated mutations affect nearly every catalytic and protein–protein interaction domain of LRRK2 [10,22] (Figure 1). These findings also point to the idea that LRRK2, through its multiple domains, might serve as an upstream central integrator of multiple signaling pathways that are crucial for proper functioning of neurons. A molecular understanding of how LRRK2 interacts with its neuronal signaling partners and transduces cellular signals is likely to reveal novel therapeutic targets, in addition to LRRK2 itself, for the treatment of PD.

LRRK2 – a multidomain, multifunctional protein

The *LRRK2* gene contains 51 exons and its encoded protein is unusually large (2527 amino acids). *LRRK2* mRNA is expressed throughout the brain and other organs [6], with *in situ* hybridization in mice revealing expression predominantly within regions of the basal ganglia that are associated with motor dysfunction in PD, and within non-motor areas such as the hippocampus [23,24]. The *LRRK2* paralog *LRRK1* encodes a large

Table 1. Summary of LRRK2 pathogenic and putatively pathogenic mutations[a]

Nucleotide change	Location	Amino acid substitution	Demonstrated disease segregation	Number of probands	Population origin	Amino acid conservation across vertebrates	Domain	Refs
2378G>T	Exon 19	R793M	NR	3[b]	European	Yes (except M in mouse)	Ankyrin repeat	[8]
2789A>G	Exon 21	Q930R	NR	1	European	Yes		[8]
3200G>A	Exon 24	R1067Q	NR	1	Asian	Yes	LRR	[64]
3287C>G	Exon 24	S1096C	NR	1	European	In mammals	LRR	[8]
3342A>G	Exon 24	L1114L	Yes[c]	3	European	NA	Splicing	[6,8,11]
3364A>G	Exon 25	I1122V	Yes	1	European	Yes	LRR	[6]
3683G>C	Exon 27	S1228T	NR	1	European	Yes (except N in chicken)	LRR	[8]
4111A>G	Exon 29	I1371V	NR	1	East Indian	Yes	Roc	[71]
4321C>T	Exon 31	R1441C	Yes	4	European	Yes	Roc	[6,10,12]
4321C>G	Exon 31	R1441G	Yes	Multiple	European	Yes	Roc	[5,10,72]
4322G>A	Exon 31	R1441H	NR	2	Asian, European	Yes	Roc	[10,12]
+3A>G	IVS31	NA	NR	1	European	NA	Splicing	[12]
4541G>A	Exon 32	R1514Q	NR	1	European	Yes in mammals (Q in bony fish)	COR	[10]
+6T>A	IVS33	NA	NR	4	Asian	NA	Splicing	[64]
5096A>G	Exon 35	Y1699C	Yes	2	European	Yes	COR	[5,6]
5606T>C	Exon 38	M1869T	NR	2	European	Yes	COR	[10,11]
5822G>A	Exon 40	R1941H	NR	1	European	Yes	Kinase	[9]
6035T>C	Exon 41	I2012T	Yes	1	Asian	Yes	Kinase	[34]
6055G>A	Exon 41	G2019S	Yes	Multiple[b]	European, North African	Yes	Kinase	[8–19, 71,73]
6059T>C	Exon 41	I2020T	Yes	3	European, Asian	Yes	Kinase	[6,8,74]
7067C>T	Exon 48	T2356I	NR	1	European	No	WD40	[9]
7153G>A	Exon 48	G2385R	NR	1	Asian	No	WD40	[10]

[a]Abbreviations: IVS, intervening sequence; NA, not applicable; NR, not reported.
[b]R793M and G2019S have also been identified in control samples [8,75].
[c]The L1114L splice-site mutation was reported to co-segregate with the disease in family 32 [6]; however, further studies [8,11] have failed to demonstrate co-segregation of this mutation in other families.

protein (2052 amino acids) that has an identical domain organization to that of LRRK2 and is widely expressed within the brain and other tissues [25]. Both genes are conserved in vertebrates and appear to have diverged from a single common ancestor because *Caenorhabditis elegans* and *Drosophila melanogaster* each have only one *LRRK* ortholog [6].

Sequence analysis indicates that LRRK2 comprises several independent domains (Figure 1), including a leucine-rich repeat (LRR) domain, a Roc GTPase domain followed by its associated C terminal of Roc (COR) domain [26], a kinase domain of the tyrosine kinase-like (TKL) subfamily [27], and a C-terminal WD40 domain. The N-terminal ~900 residues are predicted to adopt the folds of armadillo repeats (residues 180–660) and ankyrin repeats (residues 690–860). The presence of multiple protein interaction domains (armadillo, ankyrin, LRR and WD40) suggests that LRRK2, in addition to its predicted protein kinase and GTPase activities, might serve as a scaffold for assembly of a multiprotein signaling complex. However, because these domains bind diverse proteins ranging from transcription factors to signaling proteins [28], the physiological LRRK2 binding partners cannot be predicted *a priori* and will require experimental identification.

One protein, two enzymes

LRRK2 and the related LRRK1 are unusual in that they each encode two distinct enzymes – a protein kinase and a putative GTPase – within a single polypeptide chain. Because these two activities might be linked functionally we cover them both in this section, beginning with the kinase domain.

In catalytic domains of protein kinases, a small N-terminal lobe and a larger C-terminal lobe are connected by a hinge-like region to form a cleft in which Mg^{2+}-ATP and the protein substrate bind (Figure 2a). The activation segment is a 20–35-residue sequence within the large C-terminal lobe that is found between the conserved tripeptide motifs DF/YG and APE. The majority of protein kinases require phosphorylation of the activation segment for activity [29–31]. Upon phosphorylation, the activation segment is believed to adopt an active conformation, enabling substrate access and catalysis to take place.

The PD-associated LRRK2 mutations G2019S and I2020T lie at the N-terminal boundary of the activation segment, with position 2019 corresponding to the glycine residue of the conserved DF/YG sequence. The predicted effect of these amino acid substitutions on LRRK2 function is controversial. A genetic argument, which is compatible

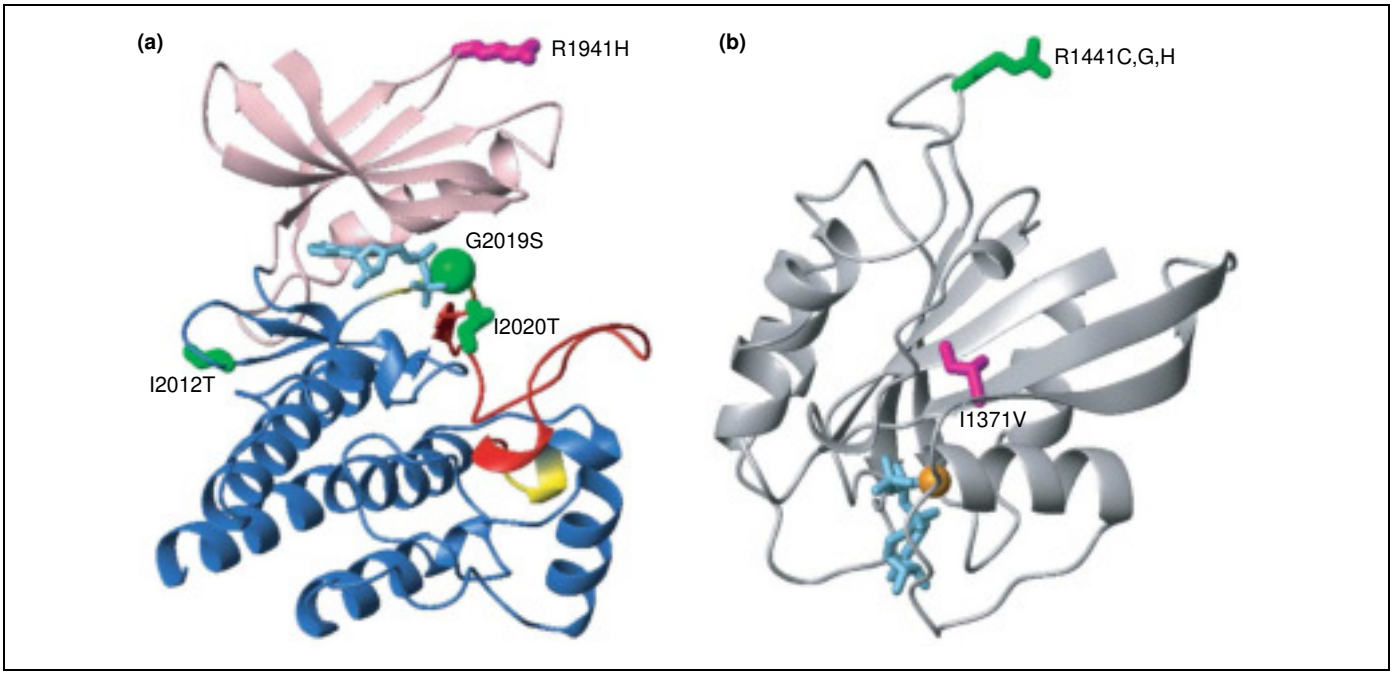

Figure 2. Homology models of the kinase and Roc domains of LRRK2. Amino acids of LRRK2 changed by putatively pathogenic *LRRK2* mutations are highlighted in magenta, whereas residues whose substitutions are known to segregate with disease are shown in green. In all cases, the wild-type side chain is depicted. **(a)** The LRRK2 kinase domain, based on the structure of the kinase domain of Lck (PDB accession code 1qpc, chain A); N-terminal and C-terminal lobes are shown in pale pink and dark blue, respectively. The positions of the pathogenic mutations G2019S, I2020T in the activation segment, and I2012T in the Mg^{2+}-binding region are indicated, along with the position of the R1941H mutation (Mg^{2+} not shown). The kinase activation loop is highlighted in red, and is flanked by the conserved DYG and APE tripeptides at the N and C termini, respectively; the APE tripeptide is shown in yellow, and the green sphere representing glycine residue 2019 indicates the end of the DYG tripeptide. **(b)** The Roc domain of LRRK2, based on the structure of the Rab7 GTPase (PDB accession code 1vg8, chain A). R1441 is on the surface of the GTPase, far from its catalytic site [indicated by a GTP analog (light blue) and Mg^{2+} (orange)]. Notes on the modeling: for each domain of LRRK2, the amino acid sequence was submitted to the Meta server (http://bioinfo.pl/Meta/) hosted by the BioinfoBank Institute of Poland [76], so that candidate parent structures could be identified and assessed. Appropriate parent structures were chosen by the degree and length of their homology to the corresponding LRRK2 domain; in some cases, the deciding factor between parent structures of equivalent homologies was the presence of a bound substrate that would elucidate the analogous binding in the LRRK2 domain. Protein information resource (PIR) alignments of each LRRK2 domain to the parent structures were obtained from simple PSI-BLAST [77] for most domains and from the FFAS03 [78] server for the WD40 domain. For each LRRK2 domain, these PIR alignments and the parent PDB files were converted into a homology model using laboratory-written software that is publicly available (http://proteins.msu.edu/Servers/Homology_Modeling/construct_homolog_PDB.html) and covered by the GNU General Public License. Ribbon illustrations of the models were generated using MOLMOL [79]. The depicted side-chains represent our best estimate of the side-chain positions, but their true position in the native structure might deviate from this position by several angstroms.

with the dominant mode of disease transmission, supports the notion that the G2019S and I2020T substitutions should have an activating, gain-of-function effect on the kinase activity of LRRK2 [17,32]. However, it has also been argued that substitution of this residue should impair kinase activity, based on the universal conservation of glycine 2019 within all protein kinases, and its apparent role in appropriate positioning of Mg^{2+} within the active site of the kinase [33]. It is noteworthy that the I2012T LRRK2 substitution lies within the predicted Mg^{2+}-binding region of the kinase domain [34].

Recent biochemical studies have yet to resolve the issue. Both the G2019S [35] and the I2020T [36] LRRK2 variants showed *in vitro* activity that was enhanced (modestly) over a low level of wild-type kinase activity. By contrast, a LRRK1 variant harboring the amino acid substitution equivalent to I2020T in LRRK2 displayed reduced *in vitro* kinase activity [25]. Notably, LRRK1 and LRRK2 share 70% sequence similarity within their kinase, Roc and COR domains. In all three studies [25,35,36], despite the substantial quantities of immunopurified LRRK proteins, the corresponding phosphorylation activity appears to be low, making it difficult to quantify activity differences among mutant forms. These apparently low activities might indicate that an important cofactor or stimulus is absent. The lack of an appropriate physiological substrate might also mask the true specific activity of the LRRK protein kinase. Alternatively, if the large multidomain LRRK depends on chaperones for proper folding and activity, it is possible that only a fraction of the overexpressed LRRK is functional. Indeed, LRRK2 has been shown to interact with heat-shock protein 90 and its kinase-specific co-chaperone, Cdc37 [36]. Correlation of the *in vitro* kinase activity of LRRK2 with its signaling activities within cells will be required to assess the potential utility of LRRK2 kinase inhibitors as drugs for treating PD.

Considering LRRK2 in the context of evolutionarily related protein kinases might be informative. Based on sequence similarity within its protein kinase domain, LRRK2 belongs to the TKL subfamily of human protein kinases [27], whose members show sequence similarity to both serine/threonine and tyrosine kinases. However, all experimental evidence to date indicates that the TKL members are *bona fide* serine/threonine kinases. The LRRK kinase domains most resemble receptor-interacting protein kinases (RIPKs), which are crucial sensors of cellular stress. The four best-studied RIPKs, which are found only in vertebrates, seem to transduce the nuclear translocation of the transcription factor nuclear factor-κ B (NF-κB) and to activate mitogen-activated protein kinase (MAPK) pathways [37]. The best-characterized MAPKs are extracellular signal-regulated kinase (ERK), c-Jun amino terminal kinase (JNK) and p38 MAPK [38,39]. Diverse extracellular stimuli provoke evolutionarily conserved MAPK pathways, which are three-tiered cascades comprising a MAPK kinase kinase (MAPKKK), a MAPKK and a MAPK, in which each kinase activates the successive kinase through activation-loop phosphorylation. Substrates of activated MAPKs include transcription factors and mitochondrial proteins, in addition to cytosolic proteins. Interestingly, kinase activity has not been demonstrated for all RIPKs; for example, RIPK1 retains some signaling roles, apparently independently of its kinase activity [37,40]. In light of the aforementioned *in vitro* activity experiments, the possibility that LRRK2 and LRRK1 are inherently low-activity protein kinases should also be considered. This is a crucial point to establish, because it might influence whether LRRK2 kinase inhibitors would be effective therapeutics.

The tyrosine-kinase-like subgroup includes several MAPKKKs, including the Raf proteins [41] and mixed-lineage kinases (MLKs) [42,43], which primarily activate the ERK and JNK pathways, respectively. Raf proteins and MLK3 can be activated by the monomeric GTPases Ras and Cdc42/Rac, respectively. Activation of Raf requires Ras-induced membrane targeting and multiple phosphorylation events, including activation-loop phosphorylation, and perhaps dimerization [44,45]. Likewise, Cdc42 promotes dimerization, activation-loop phosphorylation and membrane targeting of MLK3 [46–48]. The similarity of LRRK2 to these kinases suggests that they might share some aspects of regulation. Indeed, recent studies indicate that LRRK2 can self-associate and autophosphorylate *in vitro* [36]. However, the sites of autophosphorylation, and whether these events are interdependent, are unknown.

Because multiple members of the TKL family are activated by small GTPases, it has been hypothesized that LRRK2 kinase activity might be regulated by its putative Roc-GTPase domain in an intramolecular fashion [25,26]. Human LRRK1, which is closely related to LRRK2, binds GTP through its Roc GTPase domain, and GTP modestly stimulates LRRK1 autophosphorylation *in vitro* [25]. However, formal demonstration of GTP hydrolysis activity of either LRRK1 or LRRK2 is currently lacking. It also remains to be determined whether LRRK2 is regulated in a similar fashion and, ultimately, the guanine nucleotide exchange factors (GEFs) that activate the putative LRRK2 GTPase will need to be identified.

Three LRRK2 amino acid substitutions lie within the predicted Roc-GTPase domain at residue R1441 (R1441C, R1441G and R1441H; Figure 2b). The LRRK2 Roc-GTPase model (Figure 2b) reveals that the positively charged arginine residue 1441 is distant from the site of GTP hydrolysis, and instead is predicted to be exposed on the protein surface in a region that has been implicated in interactions with effectors and other proteins [49]. Multiple, divergent amino acid substitutions at this single, solvent-exposed site suggest that loss of protein interaction is a likely pathogenic mechanism. LRRK1 variant proteins that have mutations corresponding to the PD-linked R1441C and R1441G mutations of LRRK2 transplanted into their Roc-GTPase domain (i.e. K745C and K745G, respectively) retained their ability to bind GTP, as would be predicted from the molecular models, but they apparently had lower GTP-stimulated protein kinase activity than wild-type LRRK1 [25]. Interestingly, LRRK1 that has the substitution F1021C in the tandem COR domain (corresponding to the PD-associated LRRK2 mutation Y1699C) retained GTP-binding activity but lacked protein kinase activity [25].

Monomeric GTPases (Box 1) are crucial in signal transduction and cellular processes. Whereas the

Box 1. GTPases act as binary switches

Small GTPases of the Ras superfamily act as binary switches, cycling between a GTP-bound and a GDP-bound form (Figure I). They hydrolyze GTP, although their intrinsic enzymatic activities are not robust and their cellular role is not to produce GDP *per se*. Rather, the conformation of the GTPase dramatically changes depending on which form of nucleotide is bound. Only the GTP-bound 'active conformation' is competent to bind cellular effectors leading to signal transduction. In physiological systems, the GTPases are regulated by GTPase-activating proteins (GAPs) [69] and guanine nucleotide exchange factors (GEFs) [70]. GAPs promote the hydrolysis of GTP to GDP, thus promoting the inactive state. GEFs, which preferentially bind the GDP-bound GTPase, promote the dissociation of bound nucleotide and, because the cellular concentration of GTP vastly exceeds that of GDP, favor adoption of the active GTP-bound state.

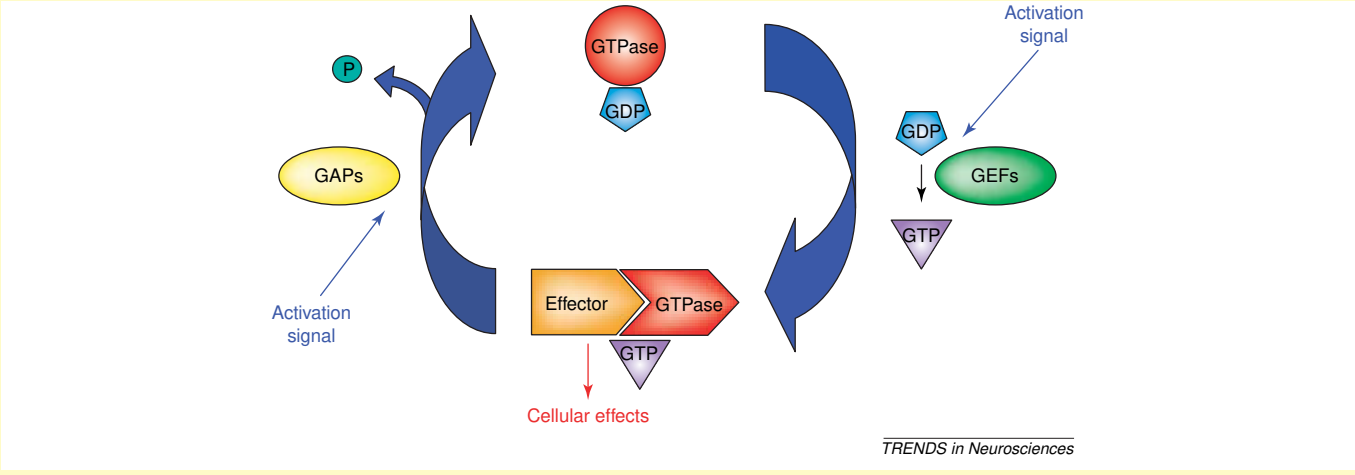

Figure I. GTPases act as binary switches.

founding member Ras is involved primarily in cellular proliferation [50], the Rho family GTPases [51,52], which include Cdc42, Rac and Rho, influence cytoskeletal rearrangements, and the Rab family members [49] are involved in vesicular trafficking.

The putative GTPase domain of LRRK2 belongs to the Roco family [26], in which the predicted GTPase (Roc) is always found in tandem with the COR domain, the function of which is unknown. This Roc–COR module is conserved throughout evolution, suggesting the functional interdependence of the two domains. Of the GTPases that have been investigated, the Roc-GTPase domain of the LRRK2 resembles most closely the Rab family of GTPases, which have been implicated in vesicular trafficking and transport [49].

Intriguingly, LRRK2 can apparently interact with the E3 ligase parkin through its COR domain [53]. E3 ligases target specific substrates for ubiquitination, generally resulting in substrate degradation through the 26S proteasome [54]. As yet there is no evidence that parkin promotes the ubiquitination or degradation of LRRK2 [53], but dysregulation of ubiquitin-mediated protein degradation has been implicated in PD, and mutations in the gene encoding parkin cause juvenile autosomal-recessive PD [55,56].

LRRK2 protein-interaction domains and PD-associated mutations

LRRK2 contains multiple sets of internal repeats, each of which is predicted to adopt a distinct structure. Such repeats, which occur in 14% of all prokaryotic and eukaryotic proteins [57], commonly serve as platforms for protein interactions [28]. The N-terminal region of LRRK2 contains seven predicted ankyrin repeats, each of which forms two antiparallel helices followed by a β-hairpin or loop (Figure 3a). The repeats stack together to form a gently curved structure in the ankyrin repeat domain [58]. Ankyrin repeats are found in diverse bacterial and eukaryotic proteins, including cytoskeletal proteins, transcription factors, signaling proteins and cell-cycle regulators. The putative PD-associated mutation R793M maps to the ankyrin repeat domain of LRRK2. Interestingly, disease-associated mutations are present in ankyrin repeats of other proteins. For instance, in familial melanoma, several mutations are located in the ankyrin repeats of cell-cycle inhibitor p16, leading to inactivation of this tumor suppressor [59,60]. In addition, a single substitution in an ankyrin repeat of Notch3 is associated with an inherited, late-onset predisposition to stroke and dementia, known as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [61]. In this case, the mutation in Notch3 does not affect its structure, but rather appears to disrupt a protein–protein interaction [62].

Each of the 13 identified LRRs in LRRK2 is predicted to form a β-strand followed by an α-helix that line up side-by-side to form an arch-like structure classified as an LRR domain (Figure 3b). LRR domains participate in interactions with diverse proteins through binding to their extended solvent-accessible surface [28,63]. Three putatively pathogenic (R1067Q, S1096C and S1228T) and one disease-segregating (I1122V) amino acid substitutions lie within the LRR domain of LRRK2 [6,8,64]. All of these residues are indeed located towards the surface of the structure and might well interfere with protein binding (Figure 3b).

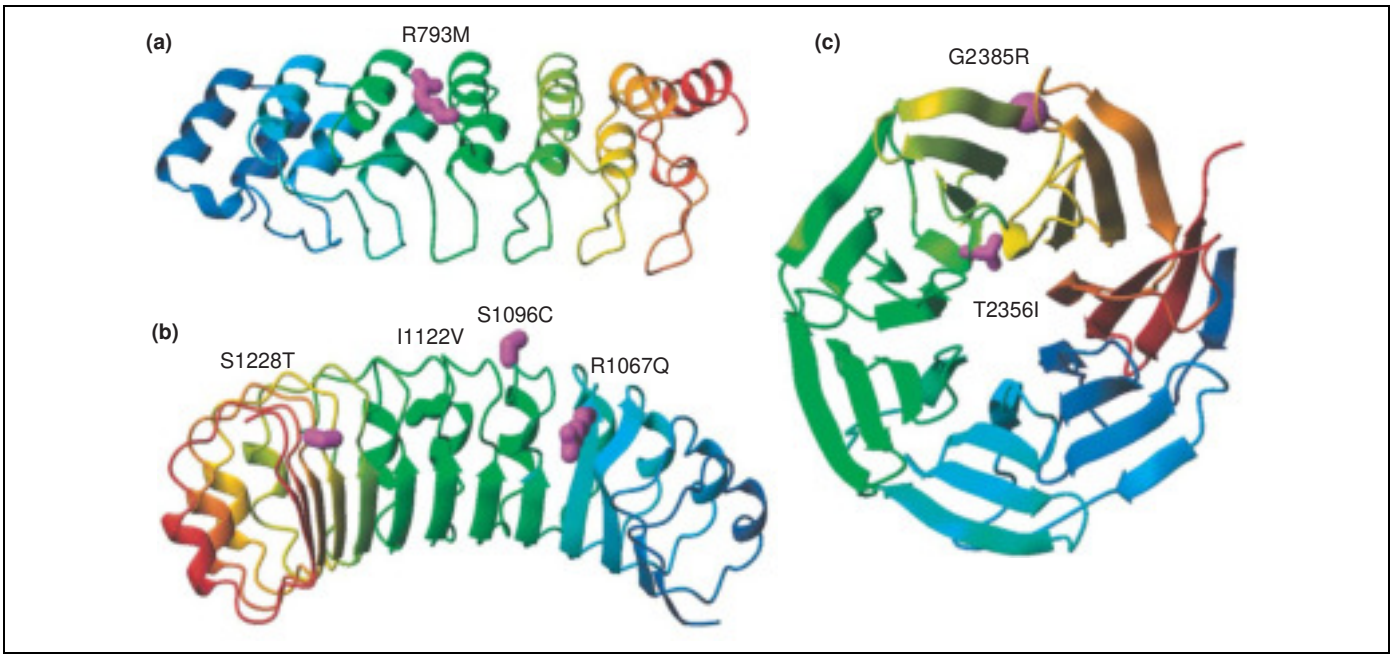

Figure 3. Homology models of the protein-interaction domains of LRRK2. Amino acids of LRRK2 changed by putatively pathogenic *LRRK2* mutations are highlighted in magenta, whereas residues whose substitutions are known to segregate with disease are shown in green. In all cases, the wild-type side-chain is depicted. In all models, the ribbon is colored from blue (corresponding to the N terminus) through the spectrum to red (corresponding to C terminus). **(a)** The ankyrin repeat domain of LRRK2, based on the structure of gankyrin (PDB accession code 1ivx, chain A). **(b)** The leucine-rich repeat (LRR) domain of LRRK2, based on the structure of internalin A (PDB accession code 1o6s, chain A), has 13 clearly identifiable LRR repeats. **(c)** The WD40 repeat domain, based on the structure of the transcriptional repressor Tup1 (PDB accession code 1erj, chain A), which adopts a seven-bladed β-propeller fold.

WD40 domains, the most common repeats found in human proteins, have been identified in functionally diverse proteins including the G_{β} subunit of heterotrimeric G proteins, transcriptional regulators, protein phosphatase subunits, RNA processing complexes, cytoskeletal assembly proteins, and proteins involved in vesicle formation and trafficking [65]. Certain WD40 domains, such as those found in yeast Cdc4, function as phosphoserine/phosphothreonine binding domains [66,67].

Despite the functional diversity of WD40-containing proteins, the 3D structures of the WD40 domain are well conserved. Each repeat contains a four-stranded, antiparallel β-pleated sheet and together these repeats form a circular bladed propeller-like structure. The predicted WD40 domain of LRRK2 comprises seven WD40 repeats (Figure 3c). This seven-bladed propeller is thought to form a rigid platform for reversibly interacting with proteins, possibly including those that contain other WD40 domains [68].

Two amino acid substitutions that have been associated with PD fall within the predicted WD40 domain [9,10]. Modeling suggests that G2385R lies on the surface of one of the propeller blades, whereas T2356I resides within a less exposed part of the domain (Figure 3c). However, neither of these substituted amino acids is conserved across vertebrates. Further experimentation will be required to determine the effects of these mutations on the function of LRRK2 and to assess their contribution to PD.

Because both LRR and WD40 domains bind diverse proteins, the binding partners of these domains in LRRK2 will have to be identified experimentally. Interestingly, the LRR and WD40 domains are unusual in that they have a high net positive charge (+20 and +21, respectively, at physiological pH) deriving mainly from conserved arginine residues. These conserved, positively charged amino acids are not found in the corresponding domains of LRRK1. In the LRR domain of LRRK2, the conserved positive charges are clearly localized on one face. It is possible that the LRR and/or the WD40 domains bind to negatively charged proteins, phospholipids or nucleic acids.

Concluding remarks

Identification of mutations in *LRRK2* that cause autosomal-dominant parkinsonism closely resembling idiopathic disease represents a new chapter in PD research. Pleomorphic pathology associated with mutations places LRRK2 further upstream in the cascade of disease pathogenesis than proteins encoded by genes previously linked to parkinsonism. Therapeutic strategies directed against this protein, to slow or even halt disease progression, might be applicable to a broad spectrum of PD and related disorders, including tauopathies such as progressive supranuclear palsy (PSP) and cortical basal degeneration (CBD). The unique multidomain organization of LRRK2 theoretically provides multiple routes for strategic therapeutic intervention. The complex challenge now is to understand how these domains interact with each other and other proteins, how the pathogenic mutations affect protein function, and which pathway(s) are involved in PD. In this way, LRRK2 might lead us to effective new therapeutic approaches for the treatment of Parkinson's disease.

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