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REVIEW ARTICLE

LRRK2 and Parkinson's disease: from genetics to targeted therapy

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Abstract

LRRK2 variants are implicated in both familial and sporadic PD. *LRRK2*-PD has a generally benign clinical presentation and variable pathology, with inconsistent presence of Lewy bodies and marked Alzheimer's disease pathology. The mechanisms underlying *LRRK2*-PD are still unclear, but inflammation, vesicle trafficking, lysosomal homeostasis, and ciliogenesis have been suggested, among others. As novel therapies targeting LRRK2 are under development, understanding the role and function of LRRK2 in PD is becoming increasingly important. Here, we outline the epidemiological, pathophysiological, and clinical features of *LRRK2*-PD, and discuss the arising therapeutic approaches targeting LRRK2 and possible future directions for research.

Introduction

Parkinson's disease (PD) is the fastest-growing neurological condition worldwide, with 12–17 million PD patients projected by 2040.[1] Despite these alarming data, no disease-modifying therapy is currently available for this devastating disease. Most clinical trials on potential disease-modifying drugs so far have treated PD as a single entity, which may have contributed to their failure. With our evolving understanding of the genetic and pathophysiological basis of PD, new approaches targeting specific genetic subtypes of PD are emerging.[2,3]

One of the most common genetic risk factors in PD is variants in leucine-rich repeat protein kinase-2 (encoded by *LRRK2*).[4] In 1978, autosomal dominant PD patients were observed over five generations in a Japanese family,[5] and in 2002 linkage analyses in this family identified the disease-associated locus, *PARK8*.[6] A mutation in the *LRRK2* gene, p.I2020T, was identified in this locus, and other variants associated with PD have been identified in the same gene in 2004.[7,8] *LRRK2* variants account for ~4% of familial PD up to 36% in some ancestries and ~1% up to 39% of sporadic PD.[9,10] One of the most frequent *LRRK2* mutations in PD is p.G2019S,[9] albeit uncommon in certain populations. In Asians, for example, p.G2019S is rare whereas p.G2385R and p.R1628P are most frequently associated with PD.[11] A common *LRRK2* haplotype, p.N551K-p.R1398H-p.K1423K, is associated with decreased risk for PD across different populations.[4,12–14]

In this review, we describe the current knowledge about genetic variants, structure, suggested mechanisms, pathology, and phenotype. We finally discuss the therapeutic approaches under development targeting LRRK2 and possible future directions for research.

LRRK2 Protein Structure, *LRRK2* Variants, and Ethnic Distribution

The LRRK2 protein is a multi-domain enzyme including catalytic kinase, armadillo, ankyrin, leucine-rich repeats, C-terminal WD40, and GTPase domains (Fig. 1).[15,16] The latter consists of a Ras-like GTPase called ROC (Ras of complex) and a dimerization domain called COR (C-terminal of ROC).[17,18]

p.G2019S and p.I2020T are located within the kinase domain, and they seem to directly increase LRRK2 kinase

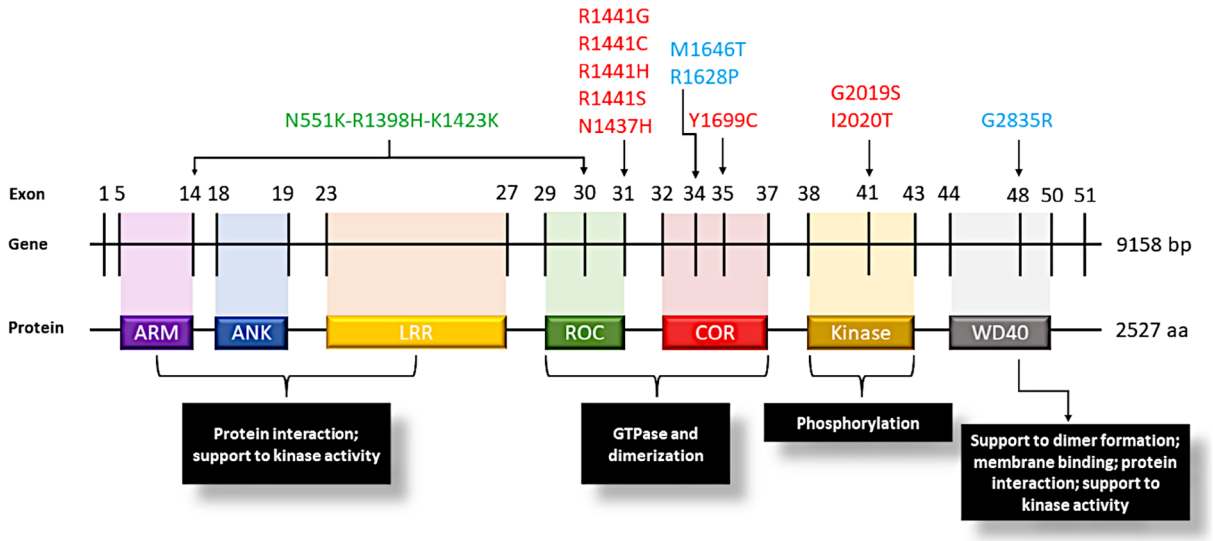

Figure 1. Schematic representation of *LRRK2* gene and LRRK2 protein with its functional domains. *LRRK2* pathogenic variants are indicated in red, risk variants in light blue, the protective haplotype in green. aa, amino acids; ANK, ankyrin repeat region; ARM, armadillo repeat region; Bp, base pairs; COR, C-terminal-of-Roc domain; Kinase, protein tyrosine kinase-like domain; LRR, leucine-rich repeats; ROC, ras-of-complex GTPase domain; WD40, WD40 repeat region.

activity. p.G2019S is a dominantly inherited variant with reduced penetrance, very common among Ashkenazi Jewish and North African Berbers, reported respectively in up to 28% and 39% of PD patients in these groups.[9] However, it is rarely observed in other groups such as East Asians.[11] Other confirmed pathogenic, dominant variants in PD are p.N1437H and p.R1441G/C/H/S, located in the ROC domain, and p.Y1699C in the COR domain.[19,20] These variants seem to also increase LRRK2 kinase activity, albeit indirectly by compromising the GTPase function.[18,21]

Additional *LRRK2* variants have been reported as risk factors for PD. For example, p.R1628P and p.G2385R, located respectively in the COR and WD40 LRRK2 domains, are the most frequent risk variants in the East Asian PD population,[22,23] increasing PD risk by about twofold,[4,24] Another population-specific variant is p.M1646T, a common variant associated with a mild increase in PD risk in Europeans, but not in Asians or Arab-Berbers,[4,14,25] This variant is located in the COR domain of LRRK2, and it was reported to be associated with an increased GCase activity,[4,25] Finally, an intergenic variant, rs76904798, located at the 5′ end of the *LRRK2* region, is associated with increased expression of LRRK2 and with a higher hazard ratio in PD patients for progression to stage three of the Hoehn and Yahr scale (H&Y).[26–28]

In contrast, *LRRK2* p.N551K-p.R1398H-p.K1423K is a common haplotype associated with a reduced risk for developing PD.[4,12–14] It has been observed across populations (Europeans, Asians, and Berbers) and is associated with reduced LRRK2 kinase activity,[13] opposite to the *LRRK2* deleterious variants. Located in the ROC domain, p.R1398H appears the most likely variant driving this association.[4,12]

LRRK2 penetrance and putative genetic modifiers

LRRK2 penetrance in PD is incomplete and age-dependent, ranging from 17% up to 85%, with no sex differences.[9,11] Variants in *MAPT*[29,30] have been reported to increase PD risk in *LRRK2* variant carriers, but this effect has not been confirmed elsewhere.[31] In a genome-wide association study, the SNP rs77395454 in *CORO1C* was associated with PD penetrance among *LRRK2* carriers, and showed an interaction at the protein level with LRRK2 kinase using co-immunoprecipitation.[30] Variants in the *GAK*[30,32] and *PARK16*[30,33] loci have also been suggested to modify both *LRRK2*-PD penetrance and age at onset (AAO), whereas *DNM3* variants have been associated with decreased *LRRK2*-PD AAO.[31] However, further studies are required to confirm and better define the role of such variants in *LRRK2*-PD penetrance and/or AAO. *DNM3* variants, for instance, were not confirmed as *LRRK2*-PD AAO modifiers in other studies and showed possible ethnic-specific effects.[34,35]

Polygenic risk score analyses comprising variants associated with PD[36] also showed an association with an increased PD penetrance in *LRRK2* variant carriers, implying that the cumulative effect of such common variants might also act as a genetic modifier.[30,37] Overall, the role of the putative genetic modifiers in *LRRK2*-PD requires further investigation to confirm their role in PD penetrance.

Pathology

The typical PD pathology is characterized by the loss of nigrostriatal dopaminergic neurons and the accumulation of phosphorylated α-synuclein (α-syn), the major component of Lewy Bodies (LBs).[38] Unlike idiopathic PD (iPD), *LRRK2*-PD does not show the typical LB pathology in about half of the cases studied,[39,40] while frequently displaying an Alzheimer's disease (AD)-like pathology with senile plaques[2] and/or phosphorylated tau-composed neurofibrillary tangles.[39,40]

As detailed in Table 1, where we summarize the pathological findings of 69 autopsies from multiple studies in *LRRK2*-PD patients, only 43/69 (62%) of these patients had LB pathology. This frequency differs between carriers of the p.G2019S variant and other *LRRK2* variants, with 76% of the former showing LB pathology, in contrast with only 41% of the latter. Tau pathology is reported in a larger proportion of *LRRK2*-PD, in 48/68 (71%) of the patients. Similar to LB pathology, tau pathology is represented differently between carriers of p.G2019S and other *LRRK2* variants, appearing in 90% and 38% of the autopsies, respectively. A study using antibodies specific for AD-type tau (co-presence of both 3 and 4 microtubule-binding repeat isoforms) demonstrated that tau pathology was found in 100% (11/11) of *LRRK2*-PD patients (LB pathology was found in 64% of them) and that AD-type

Table 1. *LRRK2*-PD pathology reported by human brain autopsies in separate studies.

Report	Autopsies (*n*)	Variants (*n*)	LB pathology (*n*+/*n*)	Tau pathology (*n*+/*n*)	Other inclusions (*n*+/*n*)
[10]	3	p.G2019S	3/3	1/3	–
139-141	33	p.G2019S	2/3	3/3	–
142	1	p.G2019S	0/1	1/1	PSP-like (1/1)
143	8	p.G2019S	8/8	6/8	–
144	3	p.G2019S	2/3	3 /3	–
145	4	p.G2019S	4/4	4/4	Olfactory bulb LBs (4/4)
146	3	p.G2019S	3/3	3/3	–
[39]	4	p.G2019S (3) p.R1441G (1)	2/4 (2/3 p.G2019S, 0/1 p.R1441G)	3/4 (3/3 p.G2019S, 0/1 p.R1441G)	–
147	1	p.G2019S	1/1	1/1	–
42,8,148	6	p.R1441C (4), p.Y1699C (2)	2/6 (2/4, p.R1441C, 0/2 p.Y1699C)	2/6 (1/4 p.R1441C, 1/2 p.Y1699C)	PSP-like (1/6, R1441C); TDP-43 (1/6, R1441C)
[53]	1	p.Y1699C	1/1	1/1	Olfactory bulb LBs
149	1	p.I1371V	1/1	1/1	–
150	2	p.R793M (1), p.L1165P (1)	2/2	2 /2	TDP-43 in TC (2/2)
139	1	p.R1441R	1/1	n.d.	–
151,152	8	p.I2020T	1/8	0/8	Glial cytoplasmic inclusions (1/8)
153	1	p.R1441G	0/1	1/1	Aß in SN
154	1	p.N1437H	1/1	1/1	Ubiquitin inclusions
155	3	p.R1441H	0/3	0/3	–
[40]	11	p.G2019S (9), p.L1165P (1), p.R793M (1)	7/11 (5/9 p.G2019S, 1/1 p.L1165P, 1/1 p.R793M)	11/11	–
156	4	p.G2019S	2/4	4/4	Ubiquitin inclusions (1/4)
TOTAL	69	–	43/69 (62%)	48/68 (71%)	–
TOTAL – p.G2019S	42	–	32/42 (76%)	38/42 (90%)	–
TOTAL – other *LRRK2* variants	27	–	11/27 (41%)	10/26 (38%)	–

Aß, amyloid beta; LBs, Lewy bodies; *n*, number of subjects; *n*+, number of subjects with the pathology; PSP, progressive supranuclear palsy; SN, substantia nigra; TC, temporal cortex; TDP-43, TAR DNA-binding protein 43.

tau is the prominent type of tau present in these patients. Abundant Aβ pathology, consistent with AD, was also found in most of the cases.[40] More rarely, *LRRK2*-PD exhibits ubiquitin-positive inclusions or the typical frontotemporal dementia pathology with TAR DNA-binding protein 43 (TDP-43) deposits,[41] or pure nigrostriatal neurodegeneration reported in p.I2020T carriers, who show a pure degeneration in about 50% of the cases.[42]

Clinical presentation

Although at the individual-level *LRRK2*-PD resembles iPD in clinical manifestations and response to therapy,[9] as a group, *LRRK2*-PD has some notable differences, including a more benign phenotype with less frequent non-motor symptoms. *LRRK2*-PD patients show a slower progression and milder cognitive impairment compared to iPD patients. They perform better in attention, executive functions and language tests, tend to develop cognitive deficits only in more advanced stages of PD, and dementia in general appears less frequently than in iPD.[9,43] Additionally, hyposmia and autonomic dysfunction are less prevalent in *LRRK2*-PD patients. Abnormal olfaction is present in 36%–49% of *LRRK2*-PD patients, compared to 75%–81% of iPD patients.[9,44,45] *LRRK2*-PD also shows a reduced frequency of orthostatic hypotension[46] and gastrointestinal dysfunction,[47] as well as greater cardiac [123I]metaiodobenzylguanidine uptake on scintigraphy,[48] compared to iPD. Another study, however, showed a similar prevalence of autonomic dysfunctions in *LRRK2*-PD and iPD.[49] While rapid eye movement sleep behavior disorder (RBD), a common prodromal symptom of synucleinopathies, is present in about 25%–58% of iPD patients, in *LRRK2*-PD it is displayed in only 0%–15% of the cases.[50–52] Whether the frequency of psychiatric symptoms, including anxiety and depression, is different in *LRRK2*-PD compared to iPD, is controversial. Some studies showed that *LRRK2*-PD patients have an increased risk of psychiatric symptoms, compared to iPD patients,[53,54] while others showed reduced risk.[55]

Although *LRRK2*-PD may display a milder phenotype compared to iPD, some characteristics could be more severe. *LRRK2*-PD patients are more prone to manifest postural instability and gait difficulty.[43] In addition, the average AAO of *LRRK2*-PD is slightly lower than iPD with a higher proportion of individuals developing PD earlier than 40 years of age.[9,56] Other differences of *LRRK2*-PD compared to iPD include a larger involvement of lower limbs in the motor dysfunction[57] and an absence of the male predominance observed in iPD.[58,59] Finally, *LRRK2*-PD shows more frequently atypical phenotypes, such as tauopathy-like symptoms, progressive aphasia and choreoathetosis.[45]

Only few attempts were made to compare the clinical phenotype between different *LRRK2* variants, typically with inconsistent results. A meta-analysis attempted to fill this gap and suggested some potential differences between carriers of the p.G2019S and p.G2385R variants. For example, p.G2019S, but not p.G2385R, was associated with dyskinesia, and p.G2385R was associated with less severe H&Y stages.[60] A systematic review showed that motor fluctuations were more frequently associated with the p.R1441C/G/H/S mutations compared to p.G2019S. Similarly, tremor and postural instability were more frequent in carriers of p.R1441G compared to p.G2019S. No other differences in motor symptoms, AAO or levodopa response emerged between *LRRK2* mutations,[61] demonstrating that, overall, it might be challenging for clinicians to distinguish the *LRRK2* mutations in individual patients based on their PD presentation.

Inflammation

LRRK2 is particularly expressed in immune cells, including lymphocytes B, macrophages, neutrophils, whereas it is substantially less expressed in the brain, except for medium-sized spiny neurons of the nucleus striatum and microglia.[62,63] Microglia arguably play a determinant role in *LRRK2*-PD neurodegeneration. In addition to their trophic function, microglial cells act as scavengers, internalizing and clearing extracellular debris, including pathological α-syn. Furthermore, they are responsible for inducing neuroinflammation by the recruitment of peripheral immune cells and release of cytokines.[64,65] α-syn is one of the triggers of such release and LRRK2 inhibition was shown to significantly mitigate this effect in human microglia cell lines.[66] In the human frontal cortex and substantia nigra, *LRRK2* expression may be modulated by microglia-specific open chromatin regions.[67]

Numerous additional lines of evidence, many of which have been extensively reviewed elsewhere,[68,69] suggested a link between LRRK2-mediated inflammation and PD development. B/T cells and CD16+ monocytes of PD patients express increased levels of LRRK2, compared to healthy controls,[19] increased levels of cytokines positively correlate with LRRK2 expression in PD patient monocytes.[70] In microglia differentiated from patient-derived iPSC, p.G2019S was shown to influence microglial activation and cytokine production in response to interferon-γ.[65]

Another hint for the relationship between PD, LRRK2 and inflammatory processes is provided by the inflammatory bowel diseases (IBDs), chronic autoimmune diseases affecting the digestive tract, including Crohn's disease (CD) and ulcerative colitis (UC). IBD patients show a 20–90% increased risk for developing PD.[71] The *LRRK2*

p.N2081D variant has been associated with an increased risk for CD and a mild increase in PD risk, and with elevated kinase activity.[72] The *LRRK2* p.N551K-p.R1398H-p.K1423K protective haplotype, in contrast, is associated with reduced kinase activity and reduced risk for both diseases.[4,72] *LRRK2* variants are also associated with leprosy, a dermato-neurological infectious disease produced by *Mycobacterium leprae*, and with type-1 reaction (T1R), one of the main complications of this disease, which causes an autoimmune response against the peripheral nerves.[73] These associations with immune and infectious diseases strengthen the notion that *LRRK2* has an important role in the immune system and inflammation which may contribute to PD pathogenesis in *LRRK2* variant carriers.

The association between *LRRK2* variants and inflammation in PD has been challenged by a recent study,[74] showing how *LRRK2*-PD patients did not differ from healthy controls in the count of any leukocyte subpopulation or neutrophil-to-lymphocyte ratio, a biomarker of systemic inflammation. These results suggest that LRRK2 might mediate immune processes through different pathways, with a more prominent role of inflammatory mediators and a dysregulation of specific immune cell subpopulations like microglia, while having a marginal effect on the number of peripheral leukocytes.[74]

Other cellular mechanisms

Multiple LRRK2-mediated mechanisms have been proposed in PD pathophysiology, including inflammation, lysosomal, autophagy, and endolysosomal trafficking dysfunction, apoptosis, ciliogenesis, and numerous others[18,75] (Fig. 2). In recent years its role in and around the lysosome has gained traction as a potentially important mechanism in PD, and in this section, we mainly focus on this role, as other mechanisms have been extensively reviewed elsewhere[18,75] and we discussed inflammation separately above. Thus far, RAB8 and RAB10 are the most validated LRRK2 substrates, while RAB29 and VPS35 are potential upstream activators.[76,77] Variants in *RAB29* and *VPS35*, but not in *RAB8/10*, have also been associated with PD risk.[36,78]

Under stress conditions, RAB29 recruits *LRRK2* to the lysosomal membranes, where it phosphorylates Rab8/10 to maintain lysosomal homeostasis.[79] *LRRK2* mutations have been associated with alteration in lysosomal morphology, distribution, pH, and function.[33,80–82] Wildtype, but not mutated VPS35 protein, rescues endolysosomal alterations driven by *LRRK2* mutations in primary rodent neurons.[33] LRRK2 also plays a key role in vesicular endocytosis and trafficking. Induced pluripotent stem cells (iPSC)-derived dopaminergic neurons from PD patients carrying the p.R1441G mutation showed impaired synaptic vesicle endocytosis (SVE), with a reduction of SVE proteins and functional synaptic vesicles, along with the accumulation of enlarged vesicles.[83] Multiple proteins phosphorylated by LRRK2 have been proposed to be involved in these processes, including endophilin A, auxilin, and synaptojanin 1.[84] In addition, mannose-6-phosphate receptor (M6PR), implicated in endosomal sorting, including the transportation of lysosomal hydrolases to late endosomes, was shown to be deficient at the lysosomes and Golgi of primary cortical neurons with p.G2019S mutation, suggesting an impairment in endolysosomal function.[33,84,85]

LRRK2 variants have also been implicated in calcium dyshomeostasis, triggering endoplasmic reticulum (ER) stress.[86,87] This effect was not observed in *LRRK2*-p.G2019S neurons, but when these were cocultured with *LRRK2*-p.G2019S astrocytes, α-syn treatment was more harmful to neurons, suggesting a cell-specific effect on astrocytes. *LRRK2* variants also affect lysosomal homeostasis, autophagy, and intra−/extracellular clearance of α-syn in astrocytes.[87]

LRRK2 is further implicated in the autophagy-lysosomal pathway (ALP), playing a role both in macroautophagy and chaperon-mediated autophagy.[88–92] *LRRK2* mutations are associated with the accumulation of ALP substrates (including α-synuclein) and autophagic vacuoles.[93,94] They are also associated with Rab10-mediated enhancement of kinesin activity, which interferes with the normal retrograde trafficking of autophagosomes and the degradation of their content within the lysosomes.[95,96] Mitophagy was also demonstrated to be affected by *LRRK2* mutations, like p.G2019S and R1441C, both associated with decreased mitophagy in multiple human cell lines including fibroblasts, DA neurons, and microglial cells.[97] In mouse brains with *LRRK2* mutation, increased LRRK2 phosphorylation of Rab8/10 enhances the activity of Rab interacting lysosomal-like proteins 1 and 2 (RILPL1/2),[98,99] which alter centrosome cohesion and ciliogenesis.[100] This mechanism was suggested to impair the signaling of neuroprotective factors sent by cholinergic neurons in the striatum to the dopaminergic neurons in the substantia nigra, with a possible increased vulnerability to neurodegeneration.[98,101] LRRK2 does not only affect mitophagy but may also be associated with mitochondrial dysfunction.[102,103] In carriers of *LRRK2* p.G2019S, mtDNA damage was found specifically in midbrain dopaminergic neurons compared to cortical neurons.[102] One explanation proposed for the mitochondrial dysfunction is the *LRRK2* variant-associated calcium dyshomeostasis, which would in turn increase the calcium influx into the mitochondria from the ER.[103]

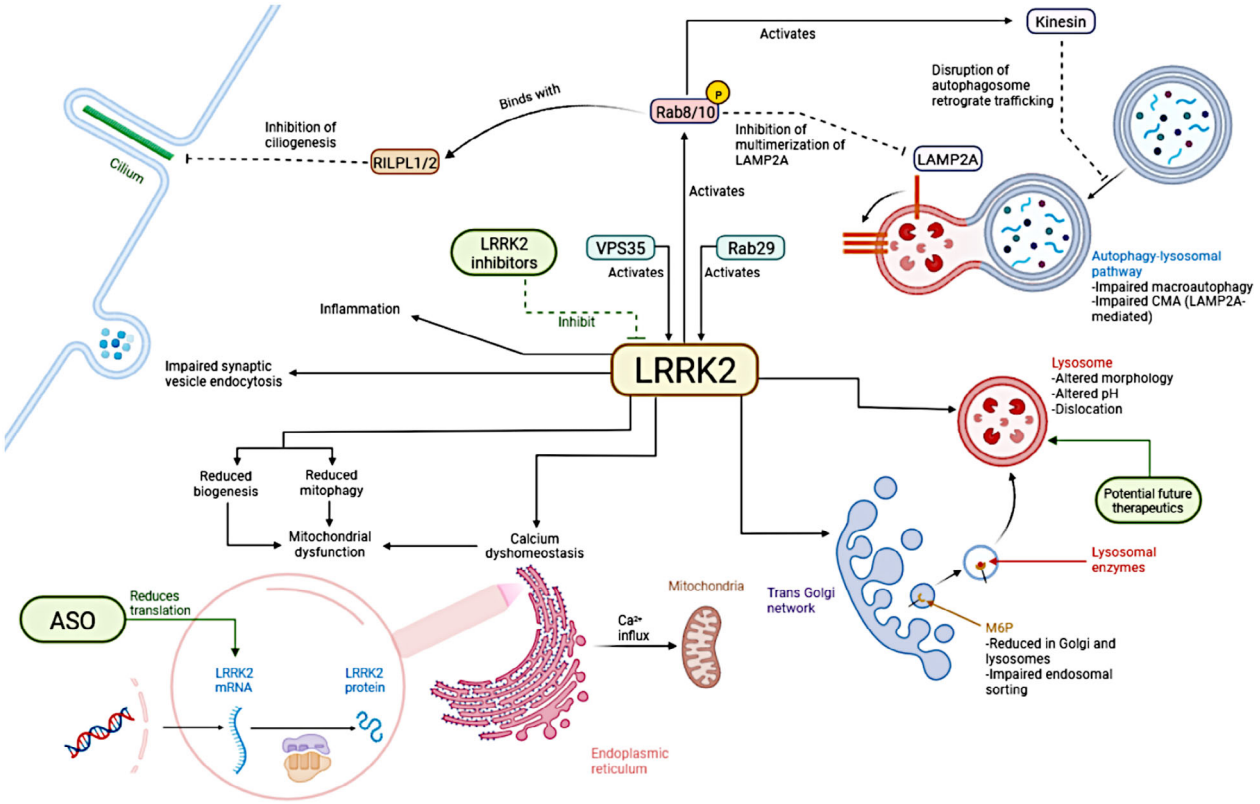

Figure 2. Principal mechanisms where LRRK2 has been implicated in Parkinson's disease and therapeutic targets. ASO, antisense oligonucleotides; CMA, chaperon-mediated autophagy; M6P, mannose-6-phosphate, deputed to transfer of lysosomal enzymes from the Golgi to the lysosome. Created with Biorender.

These data suggest that LRRK2 involvement in PD may be mediated through mechanisms including endolysosomal trafficking, autophagy dysfunction, mitochondrial dysfunction, calcium dyshomeostasis, and inflammation. These processes, like lysosomal dysfunction and inflammation, might also be interconnected with each other in PD pathophysiology.[104,105] It is possible that other mechanisms are at play, and further studies of LRRK2 are warranted to characterize them.

LRRK2 and GBA1

GBA1 variants are common genetic risk factors for PD, accounting for 5%–20% of PD patients in different populations.[106] *GBA1* encodes β-glucocerebrosidase (GCase), a lysosomal enzyme that hydrolyzes glucocerebroside and glucosylsphingosine.[107] PD patients carrying *GBA1* variants display reduced Gcase activity, and there is a large variance in Gcase activity among non-carriers of *GBA1* variants,[108,109] suggesting the existence of other modifiers of Gcase activity. The *TMEM175* T393M and *LRRK2* p.G2019S variants are such potential modifiers, as both may affect Gcase activity.[110]

It is still unclear whether *LRRK2* risk variants are associated with increased or reduced Gcase activity. One study on iPSC-derived dopaminergic neurons showed that *LRRK2* variants were associated with decreased Gcase activity, with a mechanism that would involve Rab10 phosphorylation.[111] However, in two studies performed in peripheral blood, *LRRK2* variant carriers exhibited increased Gcase activity.[25,109] These discrepant results can be explained by the different tissues that have been analyzed, that is, *LRRK2* variants might be associated with decreased Gcase activity in dopaminergic neurons and increased Gcase activity in blood cells.[25] A cell-type-specific effect of LRRK2 was further supported by a recent study that showed decreased Gcase activity in p.G2019S knock-in mouse brains and p.G2019S iPSCs-derived neurons but increased in patient-derived blood cells and fibroblasts.[112] Another hypothesis that has been suggested is that iPSCs cannot fully reproduce the aging processes happening in the human tissues, hence not fully representing Gcase activity in PD patients as they age.[25] Finally, the different methods to estimate GCase activity and divergent specificities of the substrates used in the studies can be another confounder.[25,113]

From a clinical perspective, it seems that the pathophysiology of *GBA1*-PD, characterized by a decreased Gcase activity, is different from *LRRK2*-PD. First, the clinical presentation of *GBA1*-PD is more severe than *LRRK2*-PD, with earlier onset, faster progression, and more frequent non-motor symptoms, including neuropsychiatric symptoms, RBD, autonomic dysfunction, and others (Table 2).[59,114–117] Three independent studies[118–120] also demonstrated that PD patients carrying both *GBA1* and *LRRK2* mutations manifest a milder phenotype compared to those carrying only *GBA1* variants, in contrast to what we would expect if *LRRK2* mutations further disrupted GCase activity. Moreover, the neuropathology of *GBA1*-PD resembles the typical iPD pathology with LB deposition, whereas *LRRK2*-PD often lacks this feature (Table 1).[39,40,121] Finally, while *LRRK2* variants are associated just with PD among the synucleinopathies,[122] *GBA1* variants are also associated with dementia with Lewy bodies,[116,117] a synucleinopathy that shares several features with PD, including LB deposition, but with cognitive decline preceding the motor symptoms.[123] All these differences between *GBA1* and *LRRK2* suggest that the development of *LRRK2*-PD is not connected with the GCase impairment observed in *GBA1*-PD, but other pathways might rather be involved. Furthermore, an association between *LRRK2* variants and an increased GCase activity might explain, at least in part, the milder phenotype observed in *LRRK2*-PD. It is also possible that in a subset of these patients *LRRK2* variants, and not *GBA1*, represent the main driver of the disease. Functional studies on LRRK2 kinase mechanisms of action will be necessary to address these hypotheses and clarify how *LRRK2*-PD pathophysiology differs from *GBA1*-PD.

Therapy

LRRK2-targeted treatments

The discovery that *LRRK2* deleterious variants lead to increased kinase activity[9,18] laid the foundations for LRRK2 kinase inhibitors as a potential treatment for *LRRK2*-PD (Table 3). The main LRRK2 inhibitors currently developed are DNL151 and DNL201, which already passed phase I and Ib clinical trials with most of the

Table 2. Prevalence, penetrance, pathology, and clinical features of *LRRK2*-PD versus *GBA1*-PD.

	LRRK2	*GBA1*	References
Prevalence in PD	0–39%	5–20%	[9,106,157,158]
Male/female representation	Comparable	Males overrepresented	[58,59,159]
Penetrance in PD	17–85%	10–30%	[9,11,160]
Pathology	Less frequent LBs; More frequent AD-like pathology. TDP-43 deposits, ubiquitin-positive inclusions and pure nigral degeneration have also been reported	Typical PD pathology, with LB deposition	[2,39–42]
Clinical presentation			
Motor features	Comparable to iPD	Comparable to iPD, but faster motor progression, more frequent dysphagia, dyskinesia and motor fluctuations	[9,43,116,117,161]
Cognitive decline	Less severe, later onset, dementia less frequent	More severe, earlier onset, faster progression, dementia more frequent	[9,43,116,161]
Psychiatric symptoms	Less frequent	More frequent	[53–55,161]
Autonomic symptoms	Less frequent	More frequent	[46,48,49,55,161]
Hyposmia	Less frequent	More frequent	[9,45,55,162]
RBD	Less frequent	More frequent	[59,162,163]
Longitudinal features			
Onset	Comparable to iPD or slightly earlier	Earlier	[9,56,159]
Overall progression	Slower	Faster	[9,164]

AD, Alzheimer's disease; iPD, idiopathic Parkinson's Disease; LBs, Lewy bodies; PD, Parkinson's disease; PIGD, postural instability and gait disorders; Prevalence in PD, prevalence of *LRRK2/GBA* variant carriers in PD patients; RBD, REM sleep behavior disorder; TDP-43, TAR DNA-binding protein 43.

Table 3. Clinical trials for therapeutics targeting LRRK2.

Clinical trial	Drug name	Drug type	Phase	Funding body
NCT03710707	DNL201	Kinase inhibitor	Phase Ib (completed)	Denali Therapeutics Inc. (South San Francisco, CA, USA)
NCT04056689	BIIB122/DNL151	Kinase inhibitor	Phase Ib (completed)	Denali Therapeutics Inc. (South San Francisco, CA, USA) and Biogen (Cambridge, MA, USA)
NCT05348785	BIIB122/DNL151	Kinase inhibitor	Phase IIb (ongoing)	Denali Therapeutics Inc. (South San Francisco, CA, USA) and Biogen (Cambridge, MA, USA)
NCT05418673	BIIB122/DNL151	Kinase inhibitor	Phase III (ongoing)	Denali Therapeutics Inc. (South San Francisco, CA, USA) and Biogen (Cambridge, MA, USA)
NCT03976349	BIIB094	ASO	Phase I (ongoing)	Biogen (Cambridge, MA, USA)

ASO, antisense oligonucleotides.

participants developing no or mild adverse effects at clinically relevant doses (https://www.denalitherapeutics.com, 2021).[124] An indirect mechanism proposed to control LRRK2 activity is the inhibition of its GTPase activity, which demonstrated positive outcomes both *in vitro* and *in vivo*, with reduced LRRK2 autophosphorylation and neuroinflammation, as well as suppression of neurodegeneration. Since LRRK2 is one of the only four ROC GTPases in humans, GTPase inhibitors represent promising medications in PD therapy due to their potential advantage of a greater specificity.[125] However, evidence for the involvement of LRRK2 GTPase in PD development is still not completely clear and its activity appears more difficult to modulate.[51,126] Another potential resource for LRRK2-targeted therapy is represented by antisense oligonucleotides (ASO), RNA molecules that decrease the expression or alter the splicing of LRRK2. When injected into the brain ventricles of a PD murine model with and without p.G2019S, reduced LRRK2 levels, α-syn inclusions, and nigral dopaminergic loss were observed.[127] In *LRRK2*-PD human fibroblast-deriving iPSCs, ASO restored endoplasmic reticulum Ca^{2+} homeostasis and mitophagy rate.[128] Compounds targeting specific *LRRK2* mutations are also recently under development.[129]

Safety concerns and limitations

Some safety concerns need to be addressed for LRRK2 therapy. First, along with immune cells, LRRK2 is also highly expressed in the kidneys and lungs. In mice, histopathological abnormalities have been reported in kidneys after LRRK2 inhibition[130] and, in primates, LRRK2 inhibition produced reversible lamellar bodies in the lungs, but they did not lead to any clinical manifestation.[131] In the DNL151/201 phase 1/1b clinical trials no significant alteration in the pulmonary or renal function emerged (https://www.denalitherapeutics.com, 2021).[124] In addition, loss of function *LRRK2* variants reduce LRRK2 protein levels but are not associated with any phenotypic or pathological alteration.[132] However, it should be noted that, similar to other PD therapies, LRRK2-targeted therapy will plausibly be chronic, and these experiments are not sufficiently representative of typical long-term treatments.[51] This is especially true for *LRRK2*-PD, which progresses slowly and would require unrealistically long clinical trials and large cohorts to observe the long-term effects (beneficial and/or harmful) of the therapy. Another safety concern is suggested by the role of LRRK2 in the defense from opportunistic infections.[133] In particular, LRRK2 loss of function is associated with increased vulnerability to some infections, particularly of intracellular pathogens.[134,135] The impact of a decreased LRRK2 activity on the immune system will therefore be a major aspect to consider in LRRK2-targeted therapy. Another issue to consider is the interaction of LRRK2 with GCase activity, both in the early and advanced stages of clinical trials.[2,18] As mentioned previously, the relationship between LRRK2 and GCase is controversial. If increased LRRK2 kinase activity is associated with decreased GCase activity,[111] then LRRK2 therapy might produce positive effects in PD patients with reduced GCase activity, including carriers of *GBA1* variants. However, if LRRK2 kinase is associated with increased GCase activity, as suggested by two studies in humans,[25,109] then LRRK2 therapy might have the collateral effect of reducing GCase activity, which demands caution, especially in cases when it is already impaired.

Biomarkers for LRRK2 therapy

Appropriate biomarkers to measure LRRK2 activity also need to be identified. On top of measuring the effectiveness of the LRRK2 therapy in clinical trials, they could also be employed to stratify patients based on their response and define the most appropriate dose for each subgroup. Proposed biomarkers, already used in DNL151/201 clinical trials,[124] include phosphorylation of LRRK2

substrates, such as Rab10, or LRRK2 autophosphorylation activity, both associated with LRRK2 kinase function and proven to be appropriate biomarkers to measure target engagement.[51] Another possible biomarker, potentially easier to measure on a clinical setting, is the urinary bis(monoacylglycerol)phosphate (BMP), a phospholipid localized on the late endosome and lysosomal membranes, which regulates the activity of the lysosomal hydrolases and is significantly increased in carriers of the *LRRK2* p.G2019S variant.[124,136]

Challenges in LRRK2 trial design and recruitment

When planning clinical trials for *LRRK2*, we will face several major challenges, especially around recruitment and trial design. Specifically, *LRRK2* mutations are rare, and as indicated above, carriers with *LRRK2* mutations might progress slower than others. This means that in order to see an effect on the chosen endpoint, a larger and longer trial might be required. While *LRRK2* mutations are the most common cause of autosomal dominant PD, they are still overall rare and represent a small portion of PD patients. Therefore, performing large and long trials might be challenging. This can be remedied, at least in part, by large international collaborations around these trials, some of which are already ongoing[137] (https://www.parkinson.org/advancing-research/our-research/pdgeneration).

Future perspectives

LRRK2 is a widely studied gene in PD and considerable advances have been made in our knowledge about the mechanisms that may lead to *LRRK2*-PD, but this deeper knowledge also raised new questions. Future studies will need to clarify, for example, how LRRK2 regulates the endolysosomal pathway and what is the role of primary cilia in PD pathogenesis. Furthermore, inflammation could be a determinant driver in PD development so it will be crucial to elucidate the relationship of LRRK2 with the inflammation in PD and the mechanisms that alter such relationship.

Since increased LRRK2 activity has been observed also in some iPD patients,[138] understanding the role played by LRRK2 in PD development could also further our understanding of iPD pathophysiology in some patients. It is possible that LRRK2-targeting treatments might be beneficial for this subgroup of iPD patients, and future research should test this possibility. Understanding the differences between *LRRK2*-PD from iPD might also provide key clues to comprehending PD pathogenesis and progression. For example, answering why LBs are often not observed in *LRRK2*-PD patients might shed light on other drivers of PD development.

Over the last years, considerable progress has been made on LRRK2-targeted therapy in PD. The novel drugs developed will need to address important safety concerns, especially those connected to long-term side effects, and the interactions of LRRK2 within its environment. In this regard, important information to acquire will be the relationship between LRRK2 and GCase. In fact, given that *GBA1* and *LRRK2* variants represent common genetic risk factors in PD and that personalized treatments are under development for both of these genes, understanding how LRRK2 variants modulate GCase activity will be invaluable for deciding whether LRRK2 therapy can be used in *GBA1*-PD and vice versa. Future clinical trials will need to account for these concerns to enhance the safety and effectiveness of future personalized therapy in PD.

Conclusions

In many ways, *LRRK2*-PD should be thought of as a subtype of PD mostly overlapping with iPD but with also some distinctive pathological, pathophysiologic, and clinical characteristics. The underlying mechanisms of *LRRK2*-PD are likely multiple. While inflammatory response emerges as one of the main functions of LRRK2, such protein is also arguably involved in several intracellular mechanisms, such as the endolysosomal pathway, synaptic transmission, and ciliogenesis. The progressive understanding of the relationship between LRRK2 and PD set the ground for the development of multiple therapeutic approaches that could open the doors to a novel personalized medicine in PD. Clinical trials with LRRK2-targeting treatments will still need to address several efficacy and safety concerns, and trial design challenges. Further research on the LRRK2 mechanisms involved in PD development will largely benefit from an enhancement of open science and genetic testing. This will promote a broader availability of data and increase the appropriateness and effectiveness of personalized treatment for PD.

Author Contributions

Yuri L. Sosero: conception, drafting, and review of the manuscript. Ziv Gan-Or: conception and review of the manuscript.

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Conflict of Interest

ZGO received consultancy fees from Lysosomal Therapeutics Inc. (LTI), Idorsia, Prevail Therapeutics, Inceptions Sciences (now Ventus), Ono Therapeutics, Denali, Handl Therapeutics, Neuron23, Bial Biotech, Guidepoint, Lighthouse, and Deerfield. YLS has no conflicts of interest to report.

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