Review

Genetic and environmental factors influence pleomorphy of LRRK2 parkinsonism

Vinita Ganesh Chittoor-Vinod, R. Jeremy Nichols* and Birgitt Schüle*

Department Pathology, Stanford University School of Medicine, Stanford, CA, USA
* Correspondence: bschuele@stanford.edu (B.S.), rjnichols@stanford.edu (R.J.N.)

Abstract: Missense mutations in the *LRRK2* gene were first identified as a pathogenic cause of Parkinson's disease (PD) in 2004. Soon thereafter, a founder mutation in LRRK2, p.Gly2019Ser (rs34637584), was described, and it is now estimated that there are approximately 100,000 people worldwide that carry this risk variant. While the clinical presentation of LRRK2 parkinsonism has been largely indistinguishable from sporadic PD, disease penetrance and age at onset can be quite variable. In addition, its neuropathological features span a wide range from nigrostriatal loss with Lewy body pathology, lack thereof, or atypical neuropathology including a large proportion of cases with concomitant Alzheimer's pathology, hailing LRRK2 parkinsonism as the "Rosetta stone" of parkinsonian disorders. These differences may result from interactions between LRRK2 mutant protein and other proteins or environmental factors that modify LRRK2 function, and thereby influence pathobiology. This review explores how potential genetic and biochemical modifiers of LRRK2 function may contribute to the onset and clinical presentation of LRRK2 parkinsonism. We review, which genetic modifiers of LRRK2 influence clinical symptoms, age at onset, and penetrance, what LRRK2 mutations are associated with pleomorphic LRRK2 neuropathology, and which environmental modifiers can augment LRRK2 mutant pathophysiology. Understanding how LRRK2 function is influenced and modulated by other interactors and environmental factors –either increasing toxicity or providing resilience- will inform targeted therapeutic development in the years to come. This will allow developing disease-modifying therapies for PD and LRRK2-related neurodegeneration.

Keywords: Parkinson's disease 1; parkinsonism 2; LRRK2 3; neuropathology 4; modifier 5; genetics 6; GWAS 7; environmental risk factors 8; polygenic risk score 9

1. Introduction

In 2004, missense mutations in the *LRRK2* (Leucine rich repeat kinase 2) gene were identified in the Japanese Sagamihara kindred as a pathogenic cause of Parkinson's disease (PD), as well as in families of other ethnic backgrounds across the world [2-4]. While the clinical presentation of motor symptoms of LRRK2 parkinsonism has been largely indistinguishable from sporadic PD, there is a striking difference in the age at onset (AAO), disease penetrance and neuropathological features, ranging from nigrostriatal loss with inconsistent occurrences of Lewy body (LB) and Alzheimer's pathology, lack thereof, or atypical neuropathology. These differences in the disease presentation could result from interactions between LRRK2 mutant protein and certain protein or environmental modifiers. Its clinical and neuropathological heterogeneity implicates that other factors could influence pathobiology, which might require or yield distinct therapeutic approaches. In this review, we describe 1) the clinical and neuropathological similarities and differences of LRRK2 parkinsonism with sporadic or idiopathic PD (iPD), 2) what genetic modifiers of LRRK2 including Mendelian PD genes, GWAS risk factors, and polygenic risk scores modify disease risk; 3) what LRRK2 mutations are associated with pleomorphic LRRK2 neuropathology; and 4) what environmental modifiers affect LRRK2 parkinsonism.

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1.1 Clinical presentation and incidence of PD.

PD is a common neurodegenerative movement disorder affecting dopaminergic neurons in the substantia nigra and other projection neurons in both the central and peripheral nervous system [5,6]. The overall prevalence of PD in people over 45 years was estimated at 572 per 100,000 in 2010 in the US [7]. Approximately 930,000 people in the US are affected with PD in 2020, and based on US Census Bureau population projections it will rise to 1,238,000 in 2030 [7]. Clinically, distinct motor and non-motor symptoms lead to a diagnosis of PD, although the rate of misdiagnosis is quite high with only 58% accuracy for initial diagnosis of PD [8]. Motor symptoms are comprised of bradykinesia, resting tremor, rigidity, and postural instability with asymmetrical onset of symptoms. Non-motor symptoms include loss of sense of smell, sleep/REM disorder, dysphagia, autonomic dysfunction such as constipation, urinary problems, changes in heart rate variability, and psychiatric problems with anxiety and depression as well as cognitive decline [9-11]. More men than women are diagnosed with PD. The incidence ratio is <1.2 in males and females under the age of 50, but it increases to 1.6 over 80 years of age [12]. About 10-15% of all PD patients and about 25% of early-onset PD cases in a clinical setting report a family history for PD [13].

1.2 LRRK2 variants, haplotypes, and penetrance PD

The *LRRK2* G2019S (NM_198578.3 (*LRRK2*): c.6055G>A (p.Gly2019Ser) is estimated to occur in approximately 1% of patients with sporadic PD and 3-6% of patients with familial PD in the United States, and shows the highest penetrance of all reported LRRK2 risk variants (Table 1). The LRRK2 G2019S mutation is common in the European, Middle Eastern, and North African population. There is a wide range for AAO of mutation carriers, ranging from the third to the seventh decade of life [14]. The carrier frequency in Ashkenazi Jewish PD patients is 15-20% and North African Berbers is up to 40% [15,16]. Several groups have studied the genomic background of the *LRRK2* G2019S haplotype and data suggest that there have been at least three different founding events that gave rise to the LRRK2 G2019S mutation between 1500-4500 years ago [17-19].

Penetrance for LRRK2 G2019S has been reported to be variable ranging from 24%-100% and penetrance seem to increase with age. This wide range can be accounted to differences in study cohorts, ethnic groups, presence of genetic or environmental modifiers, and recruitment or analysis methods [20,21]. In the Michael J. Fox Foundation (MJFF) Ashkenazi consortium studying 2,270 relatives of 474 cases of Ashkenazi Jewish descent, a penetrance of 26% was found [20]. Comparison of penetrance for non-Ashkenazi Jewish carriers with Ashkenazi Jewish carriers did not differ significantly, with 25% - 42.5% at age 80 [22].

Besides the LRRK2 G2019S mutation, many missense and some loss-of-function mutations have been described. However proof of pathogenicity is pending on many of these mutations owing to their rarity and scarce functional studies [19,23,24]. Importantly, loss of function mutations such as stop-codon and frameshift mutations were shown to not contribute to PD risk [24,25]. In a comprehensive meta-analysis including 94 articles covering 49,299 cases and 47,319 controls, a number of common variants were assessed for risk of developing PD. The LRRK2 A419V (Odds ratio (OR) 2.45), R1441C/G/H (OR 12.75), R1628P (OR 2.13), G2019S (OR 13.16), and G2385R (OR 2.27) were associated with increased PD risk, whereas R1398H (OR 0.81) was associated with decreased risk for PD [26] (**Table 1**).

1.3 LRRK2 domain structure and the impact of inherited mutations

LRRK2 is a large, multi-domain protein of 2527 amino acids (aa) with both GTPase and kinase enzymatic domains (**Figure 1)**. The amino terminus [1-1287aa] is not essential for intrinsic kinase or GTPase activity [27], but participates in regulation of LRRK2. The amino terminus contains armadillo and ankyrin repeats, the namesake leucine-rich repeat domain and a cluster of crucial phosphorylation residues (Ser910 and Ser935 [28,29]). Full kinase catalytic activity requires the remainder of the protein [1326-2527aa [27,30]]. This minimal catalytic fragment includes an active GTPase domain, termed Roc (Ras of complex proteins), which is juxtaposed to the COR (C-terminal of ROC) domain, classifying LRRK2 as a ROCO family protein [31,32]. The GTPase domain of LRRK2

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can be purified as an active monomer/dimer that binds and hydrolyzes GTP [33], implicating that the RocCOR domain likely participates in the dimerization of LRRK2 [34-36]. The adjacent kinase domain bears similarity to mixed lineage kinases, which are typically involved in kinase signaling cascades. The carboxy terminus contains a WD40 domain and is essential for kinase activity, where deletion of the last seven amino acids inactivate LRRK2 via disruption of the WD40 fold [27,37,38].

High-risk variants in the *LRRK2* gene encode substitutions in the catalytic core of the LRRK2 GTPase and kinase domains, (N1437H, R1441C/G/H, Y1699C, G2019S, I2020T), (**Table 1 and Figure 1**) [30,39-42]. The *LRRK2* G2019S mutation is located in subdomain VII of the kinase domain "Asp-Phe-Gly (DFG)" motif [43-45] and displays a 2-3 fold increase in kinase activity *in vitro* and *in vivo* [28,42,46,47]. Structural studies suggest that the serine substitution at position 2019 for the glycine in the DFG motif stabilizes an active state of LRRK2 resulting in the increased kinase activity [47-49]. The LRRK2 I2020T mutation displays decreased activity in some assays and increased activity in others [27,30,50,51], possibly due to substrate dependent readouts of kinase activity [52]. Mutations in the RocCor domain, N1437H, R1441C/G/H, Y1699C, are thought to disrupt GTP hydrolysis, leaving LRRK2 in a GTP bound, active kinase state, mediating increased kinase activity [33]. Non-catalytic domains of LRRK2 can also harbor PD causing mutations. The LRRK2 G2385R mutation decreases kinase activity of LRRK2 *in vitro* [27,37,38,53], but displays reduced Hsp90 interaction and 14-3-3 binding, with increased activity against Rab substrates in cells [30]. Thus, there is a correlation between PD-causing *LRRK2* mutations and an elevation in LRRK2 kinase activity, which could mediate a differential response to upstream modifiers and provide a plausible explanation for the variability in their associated PD pathophysiology.

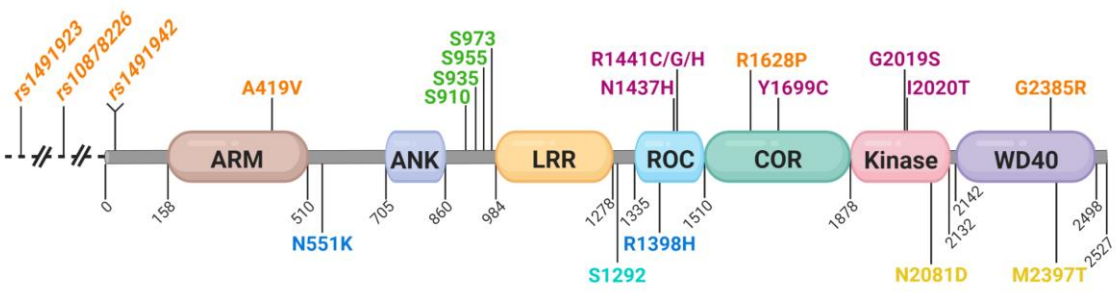

Figure 1. Domain architecture, genetic risk variants, and regulatory phosphorylation sites of LRRK2. LRRK2 is a large kinase of 2527 amino acids with multiple identifiable functional domains. High-risk variants mutations are in magenta, while risk factor variants are indicated in orange; putative protective mutations are in blue; yellow are variants associated with IBD. Regulatory phosphorylation sites are in green and LRRK2 autophosphorylation site Ser1292 is in teal. **ARM**-armadillo domain; **ANK**-ankyrin domain; **LRR**-leucine rich repeat domain; **Roc-**GTPase domain; **COR-**carboxy terminal of Roc domain**.**

1.4 LRRK2 parkinsonism: similarities and differences to iPD

LRRK2-PD has been hailed as the "Rosetta stone" of parkinsonian disorders as brains from LRRK2 cases demonstrate all major pathologies associated with parkinsonism including a large proportion with concomitant Alzheimer (AD) pathology [54-58]. However, the underlying pathways and potential disease modifier genes that explain this striking pleomorphic presentation of LRRK2-PD and variable clinical penetrance/AAO are unknown, although many cellular phenotypes and molecular pathways have been described due to altered LRRK2 signaling function [59-65], . Mendelian PD genes, GWAS risk factors, and polygenic risk scores have been nominated as influencing factors for LRRK2-PD, but studies that validate these putative modifiers are lacking.

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Table 1. LRRK2 variant overview and nomenclature

SNP (rs ID)	cDNA NM_198578.4	Protein (1-letter) XP_005268686.1	Protein (3-letter)	Odds ratio, M-H, Fixed, 95%CI	Frequency	Domain	Enzymatic impact/function
rs34594498	c.1256C>T	A419V	p.Ala419Val	2.45 [1.43, 4.2] East Asian	0.0005140	ARM	
rs7308720	c.1653C>A, C>G	N551K	p.Asn551Lys		0.08607		does not alter kinase activity
rs17466213	c.4111A>G	I1371V	p.Ile1371Val		0.001043	ROC	
rs7133914	c.4193G>A	R1398H	p.Arg1398His	0.81 [0.75, 0.89] Mixed	0.000008255	ROC	increased GTP binding and GTPase activity, deactivates LRRK2
rs74163686	c.4309A>C	N1437H	p.Asn1437His	pathogenic, low frequency	Not found	ROC	disrupts GTP hydrolysis
rs33939927	c.4321C>T/A/G	R1441C/G/H	p.Arg1441Cys/Gly/His	12.75 [3.11, 52.27]	0.000008244	ROC	disrupts GTP hydrolysis
rs33949390	c.4883G>T	R1628P	p.Arg1628Pro	2.13 (Asian)	0.000008268	COR	disrupts GTP hydrolysis, protective for T1R, but risk for PD
rs35801418	c.5096A>G	Y1699C	p.Tyr1699Cys	pathogenic, low frequency	Not found	COR	disrupts GTP hydrolysis
rs34637584	c.6055G>A	G2019S	p.Gly2019Ser	13.16 [10.16, 17.04] Mixed	0.0003873	Kinase	increased kinase activity
rs35870237	c.6059T>C	I2020T	p.Ile2020Thr	pathogenic, low frequency	Not found	Kinase	
rs33995883	c.6241A>G	N2081D	p.Asn2081Asp		0.01764	Kinase	CD/IBD risk, increased kinase activity
rs34778348	c.7153G>A	G2385R	p.Gly2385Arg	2.27 [2.03, 2.53] East Asian	0.001584	WD40	
rs3761863	c.7190T>C	M2397T	p.Met2397Thr		0.6240	WD40	CD/IBD risk allele, T1R pro-inflammatory responses

Meta-analysis for odds ratio from Shu et al. 2019, DOI: 10.3389/fnagi.2019.00013; frequency is based on Exome Aggregation Consortium (ExAC v. 1.0).

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1.4.1 Motor and non-motor features in LRRK2-PD

LRRK2-PD can present with the same cardinal motor and non-motor symptoms as sporadic PD [66]. Although the disease course and progression appears to be slightly more benign, as described in a recent meta-analysis of 66 clinical research studies evaluating the clinical phenotype of PD cases with G2019S, G2385R, R1628P, and R1441G LRRK2 mutations [67]. Overall, LRRK2-PD presents with higher rates of early-onset PD, higher female ratio and family history, which can be explained by the strong genetic contribution, although the gender effect of a higher female to male ratio may have other underlying causes. PD patients with *LRRK2* G2019S have lower depression rates and higher daily activity scores as well as better olfactory function compared to sporadic PD [26]. *LRRK2* G2019S and G2385R have a good response to a higher daily dose of L-dopa albeit more motor complications than PD non-*LRRK2* carriers. *LRRK2* G2385R affected carriers presented with milder motor scores and better cognitive function. No distinct clinical features for *LRRK2* R1628P or R1441G were detected [67]. In a large cross-sectional study, a slower decline in motor function was described among those with *LRRK2* G2019S-associated PD compared to non-LRRK2 PD [68]. Interestingly, relatives of LRRK2-PD (independent of mutation carrier status) present with a worse motor score and anxiety compared to controls, implicating other environmental or non-LRRK2 genetic modifiers might influence the penetrance of LRRK2 G2019S-PD [69,70]. Non-motor features and early predictors of PD also include reduced heart-rate variability (HRV) and cardiac sympathetic neurodegeneration [71,72]. In a study using classic HRV parameters, there was no difference between LRRK2-PD and healthy controls [73]. However, a follow-up study of the same cohort analyzed novel HRV parameters and showed that there is more vagal involvement in LRRK2-PD and even in a subset of LRRK2 non-manifesting carriers suggesting a pre-clinical endophenotype of impairment of cardiac innervation [74].

1.4.2 Cortico-striato-nigral connectivity alterations in asymptomatic *LRRK2* G2019S mutation carriers

As disease penetrance for *LRRK2* G2019S is approximately 25%, there is interest in understanding the effect of this high-risk variant in asymptomatic carriers to develop disease-specific biomarkers and endophenotypes that could support early disease detection. Functional imaging studies of asymptomatic *LRRK2* G2019S carriers compared to healthy controls have shown changes in executive function and reward-based neural processing suggesting alterations in neuronal networks and connectivity. Asymptomatic *LRRK2* G2019S mutation carriers show a reorganization of cortico-striatal circuits similar to iPD, which is more pronounced with increased age of *LRRK2* G2019S carriers. [75]. In resting-state magnetic resonance imaging (MRI), there was reduced integrity of non-motor networks detected in asymptomatic *LRRK2* G2019S before changes in connectivity of the motor network were present, which illustrate non-motor cerebral changes delineate *LRRK2* G2019S carriers as "at risk" for developing PD [76]. Another study using resting state MRI also found that altered brain connectivity precedes the onset of PD motor features. Asymptomatic *LRRK2* G2019S carriers showed functional connectivity changes in striato-cortical and nigro-cortical circuits compared to healthy controls [77]. The connectivity alterations in *LRRK2* asymptomatic carriers may represent neural compensatory mechanisms. In the Stroop color-word interference test, *LRRK2* G2019S carriers had similar behavioral performance compared to controls, but increased activity in brain regions comprising the ventral attention system [78]. In a study testing event-related functional MRI gambling task to assess the reward network, abnormal neural activity in the reward and motor networks were detected in asymptomatic *LRRK2* G2019S carriers indicating involvement of the ventral striatum [79]. Overall, these findings show that circuit structure and function in *LRRK2* G2019S carriers are already altered before symptom onset and presumably already during neuronal development and brain maturation suggesting that *LRRK2* G2019S carriers require compensatory mechanisms for normal cognitive function, which makes them potentially more susceptible to PD.

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This invokes an interesting question of whether these compensatory functional effects are related to LRRK2 modifiers and could lead to parallel pathways that also affect PD pathophysiology.

1.5 Pleomorphic LRRK2 neuropathology

The neuropathological changes that underlie the clinical PD spectrum are subtyped as PD, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), and are characterized by the formation of intracellular protein inclusions, immunoreactive for alpha-synuclein (α-syn) and its pathological forms such as phosphorylated S129 α-syn [1,39]. Neurons most vulnerable for LB pathology are projection neurons with disproportionately long axons and poor myelination, exemplified by dopaminergic neurons projecting from the substantia nigra to the striatum [5,80]. In addition, it is becoming more evident that there is overlapping pathology in older adults with up to 20% of quadruple neuropathology (tau neurofibrillary tangles, amyloid-β [Aβ], α-syn, and transactive response DNA-binding protein 43 [TDP-43]) in cases with dementia associated with a progressive course of disease [81].

After early reports of LRRK2 neuropathology in human post-mortem cases, it became apparent that LRRK2-PD presents with a heterogeneous neuropathology including pure nigral-striatal degeneration or typical LB pathology, but also cases with multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) staining with variable concomitant Alzheimer pathology [54,82,83]. This neuropathological heterogeneity cannot be explained by allelic variation in functional domains of the LRRK2 since variability has been reported for pathology associated with all variants (**Table 2, Figure 2**).

In iPD, less than 7% of cases with clinically diagnosed PD present with post-mortem neuropathological findings of pure nigrostriatal degeneration, while 77% are LB disease including brainstem predominant, transitional, and diffuse LB disease. MSA is found in 5% of clinical PD cases; and PSP, especially the parkinsonism form (PSP-P) is found in 11% of probably PD according to Hoehn &Yahr staging without dementia [1]. Notably, these numbers are quite different in LRRK2-PD cases (**Figure 2**). In LRRK2-PD, the number of cases with pure substantia nigra degeneration is 33% (24 out of 73) while cases with typical LB pathology only comprise of 38% (28 out of 73) (**Table**

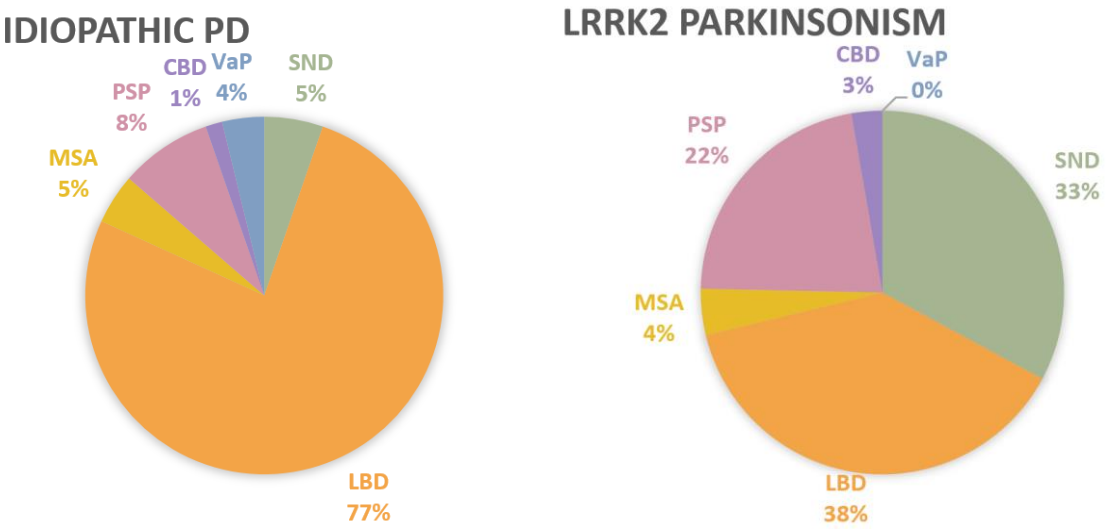

Figure 2. Frequency of neuropathologic disorders with clinical diagnosis of idiopathic PD and LRRK2-PD. Pie charts show the frequency of pathologic disorders that present with clinical parkinsonism without dementia (n=132) adapted from [1] and LRRK2-PD from cases and case series described in the literature (n=76, Table 1). Abbreviations: Lewy body disorder (LBD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), vascular parkinsonism (VaP), and substantia nigra degeneration (SND). For details on neuropathological assessment see Table 2.

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2). Mutations in the three catalytic core domains, Roc, COR, and Kinase can present with nigrostriatal degeneration, which includes R1441C, R1441H, Y1699C, G2019S, and I2020T [54-56,84].

While rare, three pathogenic LRRK2 cases with pathologically proven MSA have been described, which represents about 4% (3 out of 73 LRRK2 cases) of all reported LRRK2 cases. All cases harbored different mutations, one located in the Roc domain as LRRK2, I1371V [57], and two in the kinase domain *LRRK2* I2020T [85] and *LRRK2* G2019S [86]. Histopathologically, in MSA α-syn is found as aggregates, called glia cytoplasmic inclusions (GCI), in oligodendroglia rather than neurons, and are distinct from LBs. LRRK2 has been found in oligodendroglia in MSA and is co-localized with GCIs as well as degrading myelin sheaths, which are one of the earliest cellular abnormalities described in MSA [87]. One *LRRK2* G2019S PD case, who also carried a MAPT variant p.Q124E, has been described with occasional TDP-43 inclusions, nigral degeneration without Lewy bodies and Alzheimer-type tau pathology [88].

Approximately 22% of all LRRK2 cases (16 out of 73) have been described with neuropathological changes of hyper-phosphorylated tau resembling PSP (**Figure 2, Table 2**). PSP is a 4R tauopathy with tau aggregates in neurons and glia in specific neuroanatomical regions such as basal ganglia, diencephalon, brainstem, and cerebellum. One case with *LRRK2* R1441C, four I2020T, and five *LRRK2* G2019S cases have been described in the literature with PSP [3,89-92]. Also two cases with the risk variant *LRRK2* R1628P and one variant of unknown significance *LRRK2* A1413T have been reported with neuropathological changes compatible with PSP [93]. Two cases with LRRK2 variants (R1707K and R2618P) also show neuropathology of cortico-basal degeneration [93]

Co-existent Alzheimer pathology is well known as part of the natural history of PD. Especially in PD cases with cognitive decline, 94% of them have been described with concomitant neuropathological changes of AD, whereas cases without dementia rarely present with AD pathology [94]. In LRRK2-PD, a large proportion of cases with clinically diagnosed PD or PDD also have significant concomitant Alzheimer's disease (AD) pathology with or without LBs (12 out of 15 cases) [55,89].

In conclusion, it appears that LRRK2-PD cases with pure nigrostriatal degeneration are six times more frequent compared to iPD (33% vs 5%), whereas typical LB PD is reported at half the frequency as in iPD (38% vs 77%). MSA seems to occur at similar frequencies between LRRK2-PD and sporadic PD, but LRRK2 cases with PSP are 2.5 times higher compared to iPD (22% vs. 8%) (**Figure 2**). These striking differences in neuropathological characteristics indicate that there are likely different disease modifiers of mutant LRRK2 or environmental modifiers that affect neurodegenerative trajectories of PD and AD pathology in LRRK2-PD in specific vulnerable cell populations.

2. Environmental Modifiers of LRRK2 parkinsonism

2.1 Environmental and lifestyle factors influence penetrance and age at onset of LRRK2-PD

Environmental and lifestyle factors, head injury, and exposure to industrial toxicants including pesticides, solvents, or metals among other pollutants have been found to increase the risk for PD. Effects of these environmental exposures have been in animal models [95-97]. Some environmental factors have been associated with a decreased prevalence of PD including smoking history, caffeine and tea consumption, use of non-steroidal anti-inflammatory drugs (NSAID), and physical activity [98]. Lifestyle changes such as dietary alterations have been considered for their protective effects on neurodegenerative diseases, including AD and PD [99].

It is intriguing to hypothesize environmental or lifestyle factors also influencing risk for *LRRK2*-PD, specifically disease penetrance and AAO. Interestingly, a study showed that LRRK2 carriers with a history of cigarette smoking had a later AAO as compared to non-smokers, suggesting that smoking could modify AAO in LRRK2-PD [100]. Furthermore, regular use of NSAIDs (ibuprofen and aspirin) is associated with reduced penetrance in *LRRK2*-associated PD. This study included 259 *LRRK2*-PD and 318 *LRRK2*-asymptomatic participants. Regular NSAID use resulted in reduced risk for PD in the overall cohort (OR: 0.34) including *LRRK2* G2019S, R1441C/G, I2020T, G2385R and R1628P variants

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Table 2. LRRK2 cases with neuropathological assessment

LRRK2 mutation	Clinical presentation	Number of cases	SND	LBD	MSA	PSP	Low AD	Interm AD	High AD	CBD	TDP-43	Reference	Additional references
c.4111A>G (p.I1371V)	PD	1	-	1	-	-	-	-	-	-		[101], [54]	
	MSA	1	-	-	1	-	-	-	-	-		[57]	
c.4309C>A (p.N1437H)	PD	1	-	1	-	-	1	-	-	-		[102], [54]	
c.4321C>T/G (p.R1441C/G)	PD	6	3	2	-	1	-	-	-	-		[103]	
	PD	4	1	2	-	1	-	-	-	-		[3] [104] (Family D, R1441C)	
	PD	6	3	2	-	1	-	-	-	-		[54], [3], [103]	
c.4322 G>A (p.R1441H)	PD	3	3	-	-	-	-	-	-	-		[56]	
c.5096A>G (p.Y1699C)	PD	3	2	1	-	-	-	-	1	-		[54]	[105] (Lincolnshire, III.13), [3,106] (Fam A, III.27, III.29)
c.6055G>A (p.G2019S)	2 PD, 3 PDD	5	1	2	-	2	1	3	1	-		[24]	Johns Hopkins Brain Bank
	7 PD, 2 PDD	9	4	5	-	-	-	-	3	-		[55], [107] (3 cases)	CNDR, University Penn
	MSA	1	-	-	1	-	-	-	-	-		[86]	Brain Bank, Mount Sinai
	PSP	-	-	-	-	2	-	-	-	-		[92]	
	PD	1	1	-	-	-	1	-	-	-		[84]	Columbia
	PSP	1	-	-	-	1	1	-	-	-		[93]	
	PD	18	5	9	-	1	-	-	3	-		[54]	[108,109], 3 cases excluded from [107]
c.6059T>C (p.I2020T)	PD/MSA/PSP	9	5	1	1	4	-	-	-	-		Sagamihara kindred [54],[110], [85]	[2,90], (4 cases with tau pathology)
c.3494T>C, p.L1165P	PDD, patient E	1	-	1	-	-	-	-	1	-		[55], [111]	
c.2378 G>T, p.R793M	PD, patient D	1	-	1	-	-	-	1	-	-		[55], [111]	
c.5120G>A, p.R1707K	CBD	1	-	-	-	-	-	-	1	1		[93]	
c.4883G>T, p.R1628P	PSP/CBD	3	-	-	-	2	-	-	-	1		[93]	
c.4237G>A, p.A1413T	PSP	1	-	-	-	1	-	-	-	-		[93]	
Total cases		73	24	28	3	16	4	4	9	2			

Lewy body disorder (LBD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), substantia nigra degeneration (SND), low, medium, high AD (levels of AD pathology).

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[70]. With consortium efforts, these emerging studies in *LRRK2* cohorts will hopefully be validated and expanded for other modifying environmental factors in the future.

2.2 Increased susceptibility to synthetic toxicants in LRRK2 animal models

Environmental toxicants associated with manifestation of PD mainly comprise of inhibitors of mitochondrial complexes and/or inducers of cellular reactive oxygen species (ROS) [97]. These toxicants have been intensively investigated in animal models of PD.

1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP), a contaminant of the synthetic opiate meperidine, was identified as a neurotoxic compound leading to an acute form of parkinsonism [112,113]. Neurodegeneration associated with LRRK2 G2019S expression is augmented in mice after MPTP administration; however, mice expressing human WT LRRK2 exhibit similar response to MPTP as non-transgenic animals [114,115]. Sub-toxic exposure to MPTP increases motor impairment, dopaminergic cell loss, and astrocyte activation, which can be partially reversed by pharmacological LRRK2 kinase inhibition [115]. On the other hand, mice that lack LRRK2 kinase domain do not show any difference in MPTP sensitivity when compared to WT animals [116]. MPTP administration increases LRRK2 transcript levels together with other PD-related proteins such as Parkin, PINK1, MUL1, and USP30 in both non-transgenic rodents and rhesus monkeys [117,118] and thereby could further contribute to the neurotoxicity in LRRK2 mutant models.

Paraquat (PQ, 1,1′-dimethyl-4-4′-bipyridinium) is an herbicide that bears close structural resemblance to MPP+ and interferes with electron transport in the mitochondria to promote formation of ROS. Studies show that PQ exposure also increases motor impairment in LRRK2 over-expressing animals. Both, WT and mutant *LRRK2* variants evoke similar response to PQ in rodents [119,120]. However, knock-down of endogenous Lrrk2 leads to PQ resistance in mice and flies [119,121,122]).

Rotenone is a broad-spectrum organic pesticide and occurs naturally in several plants. Rotenone is an inhibitor of mitochondrial complex I and has been widely used for neurotoxic modeling in PD [123,124]. Mice with *Lrrk2* R1441G knock-in show clear motor deficits upon rotenone exposure, compared to WT *Lrrk2* mice treated with rotenone [125]. Studies from *Drosophila* also advocate that rotenone treatment exacerbates dopamine neuron loss and motor impairment in LRRK2 transgenic animals [126,127], although different LRRK2 variants may display variable susceptibilities towards this neurotoxin [127]. Furthermore, LRRK2 kinase inhibitors render resistance to rotenone toxicity, as seen in rats and human Wharton's jelly-derived mesenchymal stromal cells (hWj-MSCs) [128,129]. Reinhardt *et al.* showed that sensitivity to rotenone and 6-OHDA (6-Hydroxy-Dopamine) is higher in iPSC-derived midbrain dopamine neurons when G2019S mutation in introduced into the *LRRK2* locus [130]. Together, there is compelling evidence that exposure to environmental neurotoxins can act as second-hit to *LRRK2* PD pathology, thus exaggerating the associated pathology.

3. LRRK2 risk and protective variants in neurodegeneration and genetic modifiers of AAO and penetrance in *LRRK2*-PD

3.1 LRRK2 modifier risk variants

Risk variants for PD derived from GWAS or candidate gene studies have been tested in association studies in *LRRK2* cohorts. Such PD risk variants are located in *SNCA*, dynamin-3 *(DNM3)*, cyclin-G-Associated Kinase (*GAK)*, brain-derived neurotrophic factor (*BDNF)*, microtubule-associated protein tau (*MAPT)*, bone marrow stromal cell antigen 1 (*BST1)*, ras-related protein Rab-29 (*Rab29*/*PARK16)*, and vesicle-associated membrane protein 4 (*VAMP4)* (**Table 3**). While mechanistic interactions with *LRRK2* have been described in experimental studies for these risk genes [131,132], only *SNCA* and *MAPT* single nucleotide polymorphism (SNP) variants have been found to replicate in several studies (**Table 3**). Candidate gene studies of *LRRK2* modifiers for risk/penetrance and AAO have been described predominantly for G2019S, G2385R, R1628P, and other risk variants (**Table 3**). Six studies investigated the *LRRK2* G2019S mutation [133-139], two studies included *LRRK2*

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Table 3. Genetic modifiers of penetrance and age at onset in LRRK2-PD

			Association with PD risk alleles									
LRRK2 variants	**Sample size**	**Population**	**SNCA**	**DNM3**	**GAK**	**BDNF**	**MAPT**	**BST1**	**Rab29/Rab7L1**	**VAMP4**	**PD-PRS**	**Ref.**
rs1491942 (intronic)	1381 PD, 1328 ctrl	North America, Irisk, Polish	rs356219, no	N/A	rs6599388 no	N/A	rs2942168 no	rs11724635 no	rs708723 no	N/A	N/A	[140]
rs1491942, rs7133914 (R1398H)	not reported	Caucasian, Asian (GEOPD)	N/A	N/A	N/A	N/A	N/A	N/A	No	N/A	N/A	[141]
R1441C, Y1699C, G2019S, I2020T	44 carriers, 19 families	European, North American	No	N/A	N/A	N/A	rs2435207, AAO	N/A	N/A	N/A	N/A	[142]
G2385R, R1628P	231 PD G2385R, 65 PD R1628P	Chinese	No	N/A	N/A	N/A	No	No	No	N/A	N/A	[143]
G2385R	64 PD	Chinese	N/A	N/A	N/A	AAO	N/A	N/A	N/A	N/A	N/A	[144]
G2385R	53 PD	Chinese	N/A	N/A	N/A	N/A	IVS1+124C>G increased risk (major allele)	N/A	N/A	N/A	N/A	[145]
G2385R, R1628P	82 PD G2385R, 46 PD R1628P	Han Chinese	rs356219, risk & AAO (OR 1.5)	rs2421947 No	rs1564282 No	N/A	N/A	N/A	N/A	N/A	N/A	[146]
G2019S	84 PD	European	rs356219, AAO	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[133]

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LRRK2 variants	Sample size	Population	SNCA	DNM3	GAK	BDNF	MAPT	BST1	Rab29/Rab7L1	VAMP4	PD-PRS	Ref.
G2019S	84 PD	Ashkenazi	N/A	N/A	N/A	N/A	rs11079727, AAO (older in minor allele)	N/A	N/A	N/A	N/A	[134]
G2019S	101 PD	Arab-Berber	No	N/A	N/A	N/A	No	N/A	N/A	N/A	N/A	[135]
G2019S	41 families: 150 PD, 103 unaff., 232 unrelated	Arab-Berber	N/A	rs2421947, AAO earlier with GG allele	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[136]
G2019S	210 PD, 119 unaffected	European (Spain)	rs356219, AAO	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[137]
G2019S, rs10878226 (2kb upstream)	724 PD G2019S, 4882 PD rs10878226	IPDGC and other	N/A	No AAO	N/A	N/A	N/A	N/A	N/A	No	N/A	[139]
G2019S	841 (439 PD, 394 unaffected)	European, North America	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	P (OR 1.34)	[147]
	# of significant studies (# total studies)		**3 (6)**	**1 (4)**	**0 (2)**	**1 (1)**	**3 (6)**	**0 (2)**	**0 (3)**	**0 (1)**	**1 (1)**	

Table caption: SNPs included per candidate gene study: SNCA: rs11931074, rs1372525, rs181489, rs2583988, Rep-1, rs356219; DNM3: rs2421947, GAK: rs1564282; BDNF: p.V66M; MAPT: rs1052553, rs242562, rs2435207, H1/H2, IVS1+124C>G, rs393152, rs2435207, rs11079727; BST1: rs4273468; Rab29/Rab7L1: rs823144, rs823139, rs708725, rs823156, rs11240572, rs708723; VAMP4: rs11578699

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G2385R [144,145] and two studies added in addition to G2385R also the R1628P variant, which are more common variants in the Asian population [143,146]. Three studies included *LRRK2* non-coding and coding risk variants rs1491942 (intronic), rs7133914 (R1398H), and rs10878226 non-coding 2 kb upstream of *LRRK2* gene) [140,141]. Of the six studies that tested *SNCA* non-coding variants, three studies found that *SNCA* rs356219 was associated with an earlier AAO for *LRRK2* G2019S, G2385R and R1628P in European and Han Chinese population [133,137,146]. Also for non-coding variants in the *MAPT* gene, three of six studies showed either an association with disease risk or AAO [134,142,145].

Most of these clinical genetic studies of *LRRK2* modifiers have evaluated candidate genes and such studies have been challenged for their lack of replication due to small study cohorts of *LRRK2* carriers, different types of *LRRK2* alleles, and various ethnic populations. There are two pressing questions in the field: why do not all LRRK2 variant carriers develop PD (reduced penetrance) and why can the AAO be quite variable even within families (variable age at onset). GWAS studies have nominated close to 100 genetic risk loci for PD [148-153]. With large consortium efforts, it is possible to study genetic LRRK2 modifiers with adequate statistical power [154]. While single loci only contribute to a small effect on PD risk, combining individual loci allow for assessing cumulative risk represented as polygenic risk scores (PRS) and can explain ~30% of the heritable risk for PD [150]. Using a PD PRS from 89 variants reported, a large cohort of heterozygous *LRRK2* G2019S mutation carriers (833 *LRRK2* G2019S carriers: 439 PD and 394 unaffected) was analyzed and the PD PRS was associated with a higher penetrance of PD (OR: 1.34; P = 0.005). This association with PRS and penetrance was stronger in the younger individuals under 55 years (OR: 1.95; P = 0.004) [147]. The first GWAS study of penetrance and age-at-onset of PD among *LRRK2* mutation carriers included 1,879 *LRRK2* mutation carriers (853 from 294 families and 1,026 singletons; 96% G2019S carriers). A variant located in the intronic region of *CORO1C* on chromosome 12 (rs77395454; P value= 2·5E-08, beta=1·27, SE=0·23, risk allele: C) met genome-wide significance and may modify the penetrance of *LRRK2* mutations [154]. In addition, a PRS derived from publicly available PD GWAS statistics was a significant predictor of penetrance, but not of age-of-onset suggesting that common PD-associated variants collectively increase the penetrance of *LRRK2* mutations [154].

3.2 Protective LRRK2 variants in PD and MSA, but not for essential tremor or AD

Clinical genetic studies of *LRRK2* as a PD risk gene also discovered variants and haplotypes that are associated with a decreased risk for developing PD. The best-studied variant is the *LRRK2* R1398H, which has been shown in conjunction with N551K to be protective for developing PD (**Figure 1, Table 1**). This variant was first described in a multicenter study and showed that individuals carrying the *LRRK2* N551K and R1398H variants had a 20% reduced risk of developing PD [155]. These findings were replicated in several studies of Asian populations [156-159]. Additionally, a study of 177 cases with pathologically confirmed MSA and 768 controls revealed protective variants for MSA M2397T, G1624G, and N2081D [160]. However, while *LRRK2* N551K and R1398H variants seem to have a protective effect for PD, this protective effect could not be shown for essential tremor [161] or AD [162].

LRRK2 R1398H affects GTPase activity promoting axonal outgrowth and Wnt signaling activity in cell culture models and suggest that these effects are critical for neuronal maintenance and function [163]. Induced pluripotent stem cell (iPSC) lines are being made from these protective variants and further studies that elucidate protective mechanisms of *LRRK2* variants will be critical to advance understanding of *LRRK2* variant function [164,165].

3.3 LRRK2 variants in other neurodegenerative diseases

LRRK2 variants have also been tested in neurodegenerative diseases such as PSP, AD, dementia with Lewy bodies (DLB), MSA, and essential tremor and specific LRRK2 variants have also been linked to inflammatory diseases such as Crohn's disease and infectious diseases such as leprosy.

Only 1 out of 3 studies found LRRK2 variants in PSP, which included G2019S, R1441C, R1628P and a novel A1413T variant [93,166,167]. These studies suggest that PSP can present with pathogenic

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LRRK2 variants, but at a very low frequency. Furthermore, in a cohort of 772 clinical DLB patients that included cases with confirmed MSA pathology only two pathogenic *LRRK2* variants (G2019S and R1441C) were found [168]. Other studies show no association of *LRRK2* variants with MSA assessing *LRRK2* G2019S, R1628P or G2385R [169-171]. Also no significant risk of AD for *LRRK2* variants R1628P, G2385R, N551K, G2019S, and I2020T was detected in a meta-analysis including 13 studies [172] as well as no association for ET risk and *LRRK2* risk variants (L1114L, I1122V, R1441C, Y1699C, I2012T, G2019S, I2020T, G2385R) have been found [173-177]. However, the only *LRRK2* variant that has been associated with ET is *LRRK2* R1628P. This study included 1277 subjects comprising of 450 ET cases and 827 controls which showed a 2-fold increased risk for ET (OR: 2.20, P = 0.0035) [178].

Patients with inflammatory bowel disease (IBD) have a higher risk of developing PD [179]. A meta-analysis concluded that patients with Crohn's disease (CD) have a 28% increased risk of PD and similarly, ulcerative colitis patients have a 30% increased risk of PD compared to controls [180]. Gene association studies have found a genetic link between IBD and PD through *LRRK2* as a common risk gene for both diseases. Similar to PD, *LRRK2* N551K and R1398H variants are protective whereas the *LRRK2* N2081D variant increases risk for IBD (OR 1.6, $P = 2.1\times10^{-6}$) [181].

4. Summary

In the 15 years since the discovery of *LRRK2* mutations as a cause for PD, clinical and basic research has made enormous progress toward understanding the role of LRRK2 in PD. The work to date has been instrumental in the quest to develop PD preventing or modifying drugs with LRRK2 as a target. However, these efforts are not without potential downfalls, as complete inhibition of LRRK2 induces lung pathology in non-human primates that also resembles LRRK2 knock-out phenotypes in rodents [182]. Additionally, in this review, we highlight crucial distinctions of LRRK2 PD from iPD with respect to pathology and clinical presentation. We propose these differences arise from the differential effects of a variety of genetic or environmental factors. Does this present a treatment obstacle? If we approach the problem with the foreground hypothesis that differences in *LRRK2* PD from iPD are the result of how different "modifiers" exert their action on LRRK2 function, then we will gain the opportunity to not only understand how asymptomatic *LRRK2* carriers pheno-convert to PD, but also identify novel therapeutic targets and pathways that might even be relevant and translatable for iPD.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

α-syn	alpha-synuclein
Aβ	Amyloid-beta
AAO	Age at onset
AD	Alzheimer's disease
ANK	Ankyrin domain
ARM	Armadillo domain
BDNF	Brain-derived neurotrophic factor
BST1	Bone marrow stromal cell antigen 1
CBD	Corticobasal degeneration

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CD	Crohn's disease
COR	C-terminal of ROC domain
DLB	Dementia with Lewy bodies
DNM3	Dynamin-3
ET	Essential Tremor
GAK	Cyclin-G-associated kinase
GCI	Glia cytoplasmic inclusions
GTP	Guanosine triphosphate
GWAS	Genome-wide association study
HRV	Heart-rate variability
IBD	Inflammatory bowel disease
iPD	Idiopathic Parkinson's Disease
iPSC	Induced pluripotent stem cells
LB	Lewy body
LBD	Lewy body disorder
LRR	Leucine rich repeat domain
LRRK2	Leucine rich repeat kinase 2
MAPT	Microtubule-associated protein tau
MRI	Magnetic resonance imaging
MSA	Multiple system atrophy
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PSP	Progressive supranuclear palsy
PSP-P	Progressive supranuclear palsy parkinsonism
PRS	Polygenic risk score
REM	Rapid eye movement
Roc	Ras of complex proteins
SND	Substantia nigra degeneration
SNP	Single nucleotide polymorphism
TDP-43	Transactive response DNA-binding protein 43
VAMP4	Vesicle-associated membrane protein 4
VaP	Vascular parkinsonism

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