

Leucine-Rich Repeat Kinase 2 Gene-Associated Disease: Redefining Genotype-Phenotype Correlation

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Key Words

Leucine-rich repeat kinase 2 gene • Parkinson's disease • Lewy body disease • Progressive supranuclear gaze palsy • Nigral degeneration

Abstract

Background: Leucine-rich repeat kinase 2 (*LRRK2*) has emerged as the most prevalent genetic cause of Parkinson's disease (PD) among Caucasians. Patients carrying an *LRRK2* mutation display significant variability of clinical and pathologic phenotypes across and within affected families. **Methods:** Herein, we review available clinical and pathologic data on patients with an *LRRK2* mutation who have come to autopsy. **Results:** Thirty-eight patients have been reported who presented clinically with PD; parkinsonism with resistance to levodopa, supranuclear gaze palsy, or autonomic dysfunction; or tremor and dementia. Pathology showed typical PD-type Lewy body disease (LBD) in most patients, whereas in others there was 'pure' nigral degeneration (one with TDP-43-positive inclusions), diffuse LBD, or tau-, α -synuclein- or ubiquitin-positive pathology reminiscent of progressive supranuclear gaze palsy, multisystem atrophy, and frontotemporal dementia with ubiquitin-positive inclusions. **Conclusions:** Such clinical and pathologic variability suggests Lrrk2 acts upstream from other proteins implicated in neurodegeneration. Specific mutations may be associat-

ed with alternative progressive supranuclear gaze palsy-like or 'pure' nigral degeneration phenotypes. A different effect on Lrrk2 kinase activity may play a role in such heterogeneity.

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Introduction

Major breakthroughs in the genetics of Parkinson's disease (PD) have dramatically altered our understanding of the mechanisms leading to neurodegeneration [1]. As the number of genes and loci implicated in PD increased over the past decade, it has become clear that genetic factors play a significant role in risk for both sporadic and familial PD. However, such discoveries have also highlighted the clinical and pathologic variability associated with genetically determined PD. Mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene have emerged as the major genetic determinants of PD in Caucasian populations [2]. Yet carriers of a given *LRRK2* mutation even from the same family can differ in both their clinical and pathologic presentations [3]. Herein we discuss the implications of recent genetic discoveries for genotype-phenotype correlations in *LRRK2*-associated disease.

Table 1. Characteristics of *LRRK2*-associated conditions with reported pathology

First author and year	Name of family	Patients	Lrrk2 (p.) mutation	Age at onset, years	Clinical features	Pathology ¹
Wszolek, 1997, 2004; Zimprich, 2004	D	4	R1441C	48–78	P ² (3), P+S (1)	BLBD (1), DLBD (1), NFT (1), ND-Ub-TDP-43 (1)
	A	2	Y1699C	51–56	P (1), P+A (1)	ND-Ub ³
Khan, 2005	Lincolnshire	1	Y1699C	50	P	LBD (few cortical LB)
Gilks, 2005	–	3	G2019S	41–70	P	LBD ⁴
Rajput, 2006	SK	1	G2019S	78	P ⁵	NFT
Ross, 2006	–	8	G2019S	41–79	P (3), P+Au (2), P+Au+D (1), DLB+Au (1), DLB (1)	BLBD (4), TLBD (3) ⁶ , DLBD (1)
Giasson, 2006	–	3	G2019S	47–76	P (2) ⁷ , P+D (1)	LBD (2) ⁸ , ND ⁹
Dachsel, 2007	–	1	G2019S	NR	D, T	FTLD-U pathology
Gaig, 2007	–	1	G2019S	61	P	ND
Gaig, 2008	–	1	G2019S	51	P	LBD (few cortical LB)
Chen-Plotkin, 2008	–	3	G2019S	47–76	P	LBD (diagnosis: PD)
Santpere, 2009	–	1	G2019S	NR	P	LB in SN
	–	1	R1441G	NR	P	ND
Hasegawa, 2009	Sagamihara	8	I2020T	40–74	P	ND (6), ND-GCI (1), BLBD (1)

Figures in parentheses indicate number of cases. A = Amyotrophy with fasciculations; Au = autonomic dysfunction; D = dementia; LB = Lewy bodies; ND = nigral degeneration; ND-GCI = nigral degeneration with α -synuclein-positive glial cytoplasmic inclusions (i.e. multisystem atrophy pathology); ND-Ub = nigral degeneration with ubiquitin-positive cytoplasmic and nuclear inclusions; NFT = neurofibrillary tangles, pathology reminiscent of progressive supranuclear gaze palsy; NR = not reported; P = levodopa-responsive parkinsonism similar to that of idiopathic Parkinson's disease; S = supranuclear gaze palsy; SN = substantia nigra; T = tremor; TLBD = transitional Lewy body disease.

¹ All patients had SN neuronal loss and gliosis. ² One patient died before levodopa became available. ³ One patient with concurrent AD pathology, and 1 with mild motor neuron loss in lumbar spinal cord. ⁴ Two with LB in limbic cortex, 1 with mild AD pathology. ⁵ Poor response to levodopa. ⁶ One with concurrent AD pathology. ⁷ One did not tolerate levodopa. ⁸ One with concurrent AD pathology, and LB and Lewy neurites in the neocortex, and 1 with sparse LB, senile plaques and NFT in neocortex. ⁹ Rare NFT and senile plaques in neocortex.

***LRRK2*-Associated PD**

The most prevalent mutation in *LRRK2* (p.G2019S) accounts for 1–2% of sporadic PD and about 5% of familial PD in populations of European descent. Figures rise to 10–40% among North-African Arabs and Ashkenazi Jews, whereas *Lrrk2* p.G2019S is almost absent in Asian populations. Over forty *LRRK2* variants have been identified in PD patients, but only six of them (p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, and p.I2020T) have been established as definitely pathogenic [4]. The penetrance is reduced and age dependent, with ~75% of mutation carriers displaying clinical PD by age 80 [1, 5]. Two common variants in *LRRK2* (p.G2385R and p.R1628P) were found to increase risk for sporadic PD in Asian populations [6, 7].

Clinically, the majority of PD patients carrying a mutation in *LRRK2* display classic levodopa-responsive late-onset parkinsonism similar to that of idiopathic PD, although a more benign course has been suggested [5]. However, there are notable exceptions. In two of the families that led to the discovery of *LRRK2*, some patients presented with atypical features such as amyotrophy and fasciculations, autonomic dysfunction, supranuclear gaze palsy, dystonia or dementia [8, 9]. Additionally, patients with the *Lrrk2* p.G2019S and p.R1441H mutations have been reported with variable phenotypes including corticobasal syndrome [10], progressive supranuclear gaze palsy (PSP) [11], dementia with tremor [12] and levodopa-resistant parkinsonism [13].

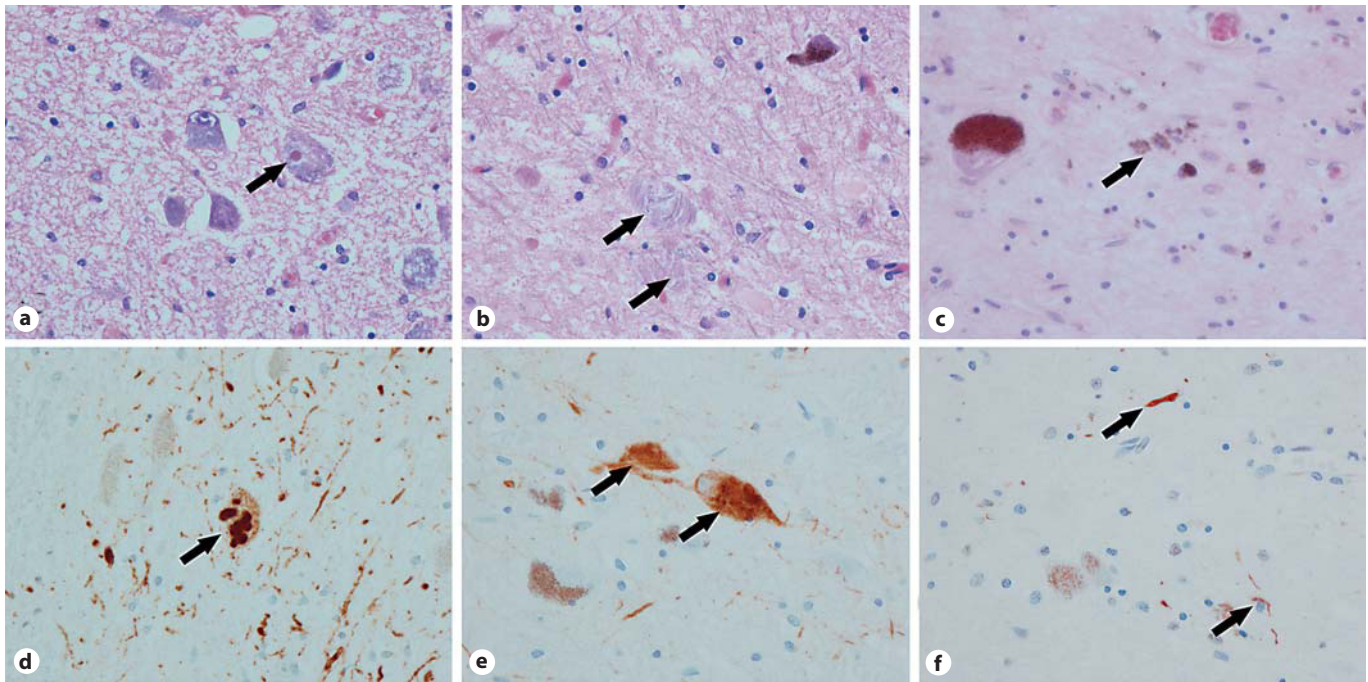


Fig. 1. Histology and immunohistochemistry of 4 PD patients from family D carrying the *Lrrk2* p.R1441C mutation. **a, d** DLBD. **b, e** Tauopathy. **c, f** 'Pure' nigral degeneration. **a** Lewy body in periaqueductal gray (arrow; HE). **b** Extracellular neurofibrillary tangles (arrows; HE) in substantia nigra. **c** Nonspecific neuronal loss

with neuromelanin in macrophages (arrow; HE). **d** Lewy bodies in periaqueductal gray (arrow; α -synuclein). **e** Neurofibrillary tangles in substantia nigra (arrows; phospho-tau). **f** Neurites in substantia nigra (arrows; TDP-43).

Neuropathology of *LRRK2* Mutation Carriers

Only 38 autopsies of diseased individuals carrying a proven pathogenic *LRRK2* mutation have been reported so far (table 1; fig. 1) [2, 3, 10, 12–21]. Most patients had the p.G2019S mutation (22/38), but some carried the p.I2020T (8/38), p.R1441C (4/38), p.Y1699C (3/38), or p.R1441G (1/38) mutation. Twenty-eight patients had typical levodopa-responsive parkinsonism, whereas others had parkinsonism with levodopa resistance (1/38), supranuclear gaze palsy (1/38), muscular atrophy (1/38), dementia (3/38), or autonomic dysfunction (4/38); one patient had only dementia and tremor.

All patients displayed neuronal loss and gliosis in the substantia nigra. In 20 patients, pathology was deemed compatible with that of idiopathic PD (brainstem or transitional Lewy body disease – LBD, with or without moderate numbers of cortical LB), with concurrent Alzheimer's disease (AD) pathology in 3 of them (fig. 1). Interestingly, the second most common pathology was 'pure' nigral degeneration with no LB, displayed by 12 patients carrying the p.I2020T mutation (6/12) or the p.Y1699C

(2/12), p.G2019S (2/12), p.R1441C (1/12), or p.R1441G (1/12) mutation (fig. 1). In the p.R1441C carrier previously reported to have 'pure' nigral degeneration [2], we found that the ubiquitin-positive cytoplasmic inclusions in the nigra were positive for transactive response DNA-binding protein 43 (TDP-43), a feature that has not been emphasized in previous studies (fig. 1). In other patients, predominant pathological features included diffuse LBD (DLBD) (2/38), tau-positive neurofibrillary tangles reminiscent of PSP pathology (2/38), α -synuclein-positive glial cytoplasmic inclusions compatible with multisystem atrophy (MSA) (1/38), and ubiquitin-positive pathology suggestive of frontotemporal dementia (FTLD-U; 1/38). The most striking intrafamilial variability was observed in family D with the *Lrrk2* p.R1441C mutation, with brainstem LBD (BLBD), DLBD, PSP-like pathology, and nigral degeneration with ubiquitin-/TDP-43-positive cytoplasmic inclusions (fig. 1) [2, 3]. Most patients from the Sagamihara family with the *Lrrk2* p.I2020T mutation had 'pure' nigral degeneration (n = 6); however, one patient had MSA pathology and another one BLBD [16].

From Gene to Disease

LRRK2 is a 144-kb gene with 51 exons that encodes a 2,527 amino-acid multidomain protein. The physiologic function of *Lrrk2* remains largely unknown, but experimental evidence suggests it may play a role in neuritic outgrowth and branching [22]. Immunohistochemistry studies in mice and humans have shown that *Lrrk2* is mostly a cytoplasmic protein that is widely expressed in the brain and in other organs [17, 23]. While full-length *Lrrk2* is not a major component of LB, recent studies have shown that truncated forms of *Lrrk2* can be identified within LB, suggesting a potential role in protein aggregate formation [21]. Pathogenic mutations and genetic risk factors are located in the functionally relevant and highly conserved Roc, COR, MAPKKK and WD40 *Lrrk2* domains. In vitro assays have shown that mutations located in the Roc and MAPKKK domains enhance *Lrrk2* autophosphorylation, consistent with an autosomal dominant 'gain-of-function' pathogenic mechanism with increased kinase activity [24]. However, not all experimental data fit this model, which does not provide an explanation for mutations located in the COR and WD40 domains [22, 25].

Understanding the mechanisms that lead to neurodegeneration in *LRRK2* mutation carriers poses several challenging questions. The widespread expression of the *Lrrk2* protein contrasts with the prominent vulnerability of select neuronal populations such as the nigrostriatal system, suggesting interactions with other molecules displaying regional specificity. Moreover, the significant clinical and pathologic phenotypic variability found in *LRRK2* mutation carriers supports the notion that *Lrrk2* acts upstream of other proteins implicated in neuronal death, and that additional genetic, environmental and stochastic factors determine the type of pathology that develops in a given individual – α -synuclein, tau, or ubiquitin/TDP-43 positive [2, 19, 22]. The p.R1441 residue may be associated with tau pathology as one patient with the *Lrrk2* p.R1441C mutation had supranuclear gaze palsy and PSP-like pathology (fig. 1), and one p.R1441H carrier evolved into clinical PSP [2, 11]. Furthermore, the lack of specific protein aggregation in some *LRRK2* mutation carriers indicates that other pathways exist, which may include accumulation of proteins such as TDP-43 which was identified in one of our patients. Of note, half of the patients with 'pure' nigral degeneration harbor the *Lrrk2* p.I2020T mutation, which, in contrast to p.G2019S, was shown to reduce *Lrrk2* kinase activity [25]. This may suggest that increased *Lrrk2* kinase activity triggers

α -synuclein aggregation and LB formation, whereas reduced kinase activity induces nigral degeneration through other pathways. Alternatively, some of the clinical and pathological phenotypes observed may represent incidental co-occurrence of other diseases unrelated to specific *LRRK2* mutations. Such hypothesis may be valid for individuals with pathology reminiscent of MSA, PSP, AD or FTLN-U; however, it would not account for those patients with 'pure' nigral degeneration.

Conclusions

Although recent advances in the genetics of PD have provided mechanistic hypotheses for neurodegenerative pathways, a thorough understanding of disease pathogenesis will require further studies addressing the critical issues of selective vulnerability and genotype-phenotype correlation. The clinical and pathological data reviewed herein suggest specific mutations may be associated with alternative PSP-like or 'pure' nigral degeneration phenotypes. A different effect on *Lrrk2* kinase activity may play a role in such heterogeneity.

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