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Lrrk2 R1441C parkinsonism is clinically similar to sporadic Parkinson disease

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Abstract

Objective—Leucine-rich repeat kinase 2 (*LRRK2*) mutations are the most common cause of Parkinson disease (PD). Several dominantly inherited pathogenic substitutions have been identified in different domains of the Lrrk2 protein. Herein, we characterize the clinical and genetic features associated with Lrrk2 p.R1441C.

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Methods—We identified 33 affected and 15 unaffected *LRRK2* c.4321C>T (p.R1441C) mutation carriers through an international consortium originating from three continents. The age-specific cumulative incidence of PD was calculated by Kaplan-Meier analysis.

Results—The clinical presentation of Lrrk2 p.R1441C carriers was similar to sporadic PD and Lrrk2 p.G2019S parkinsonism. The mean age at onset for parkinsonism was 60 years, range 30 – 79 years; fewer than 20% of the patients had symptoms before the age 50 years, while by 75 years >90% of them had developed symptoms. Haplotype analysis suggests four independent founders for the p.R1441C mutation.

Conclusions—The distribution in age at onset and clinical features in Lrrk2 p.R1441C patients are similar to idiopathic and Lrrk2 p.G2019S parkinsonism. Several independent founders of the p.R1441C substitution suggest this site is prone to recurrent mutagenesis.

The recent discovery of mutations in the leucine-rich repeat kinase 2 (*LRRK2* [MIM *609007]) gene in clinically typical, late-onset Parkinson disease (PD) highlights the role of genetics in this disorder.[1,2] To date, pathogenicity has been demonstrated for five Lrrk2 protein substitutions (p.R1441C, p.R1441G, p.Y1699C, p.G2019S, and p.I2020T). They are located within the guanosine triphosphatase (GTPase), the C-terminal of Roc (COR), and the kinase domains of the protein. Furthermore, the p.G2385R substitution in the WD40 motif of Lrrk2 is consistently associated with increased risk for PD in the Asian population.[3–7]

The Lrrk2 p.R1441 amino acid residue in the GTPase domain is the second most common location of pathogenic Lrrk2 substitutions, after p.G2019S. The p.R1441 residue may be prone to mutagenesis as the two pathogenic substitutions (p.R1441C; c.4321C>T and p.R1441G; c.4321C>G) and one putatively pathogenic substitution (p.R1441H, c.4322G>A) affect the very same residue. An additional putative pathogenic substitution (p.A1442P; c. 4324G>C) was recently reported in the adjacent amino acid.[8]

Further clinical and genetic investigation may translate neurogenetic discoveries into improved care for patients. These studies provide a framework for advancing our understanding of the molecular pathology of parkinsonism and may guide future functional research. The present collaboration represents a worldwide initiative to collect mutation carriers and characterize clinical and genetic features of the pathogenic Lrrk2 p.R1441C substitution.

METHODS

Study population

This international consortium was formed to identify all reported Lrrk2 p.R1441C substitution carriers. A Medline search was conducted using the terms *LRRK2* and *R1441C*, including publications up to June 2007.[2,9–16] Additionally, unreported mutation carriers who had come to the attention of any of the participating centers were included. We identified 33 affected and 15 unaffected p.R1441C substitution carriers.

PD was diagnosed by movement disorder neurologists according to published criteria and all participating neurologists filled out a clinical evaluation form designed for this study (Z.K.W.).[17] If available for genetic and clinical evaluation, family members of the index case were also examined. Study instruments included the Unified PD Rating Scale and Hoehn and Yahr staging.[18,19] A summary of the clinical characteristics of the affected mutation carriers is provided in the table. The institutional review boards at each participating institution approved the study.

Genomic DNA were extracted from peripheral blood using standard protocols. Direct sequencing of exon 31 was used to verify *LRRK2* c.4321C>T (p.R1441C) mutation carrier status identified through screening procedures and to determine genotypes for adjacent single nucleotide polymorphisms (SNPs). Sequencing was performed utilizing the Applied Biosystems Big-Dye Terminator v3.1 Cycle Sequencing kit. Data were analyzed with SeqScape software version 2.1.1 (Applied Biosystems). Microsatellites were amplified by PCR using fluorescently labeled primers, run on an ABI 3730 genetic analyzer and analyzed using GeneMapper 4.0 Software (Applied Biosystems). Microsatellite allele sizes were normalized using CEPH-control DNA (1331-01 and 1331-02). Twenty-seven markers (9 SNPs and 18 microsatellites) spanning 16 Mb across the *LRRK2* locus were systematically selected to determine whether subjects carrying the *LRRK2* c.4321C>T (p.R1441C) mutation shared a common haplotype. Seventy-four mutation carriers and noncarriers from 20 families were genotyped to determine the disease-carrying p.R1441C haplotypes as shown in figure e-1 on the *Neurology*® Web site at www.neurology.org. In each family, all available individuals were genotyped to establish gametic phase. In smaller families where phase could not be established allele sharing was used to assign the most likely haplotype.

Statistical analysis

PHASE v.2.1.1 was used to estimate the frequency of the *LRRK2* c.4321C>T haplotypes in 80 Caucasian US controls previously genotyped for microsatellite markers within the *LRRK2* locus.[20,21] Haplotype frequencies were only estimated when phase could be established. The age-specific cumulative incidence of PD in affected p.R1441C substitution carriers was estimated using the Kaplan-Meier method, considering age at onset as the time variable.

RESULTS

We identified 33 affected and 15 unaffected Lrrk2 p.R1441C carriers from 20 families, including four patients with no family history of parkinsonism. Clinical features were comparable to typical, late-onset sporadic PD including all four cardinal signs of PD (tremor, bradykinesia, rigidity, and postural instability). The age-specific cumulative incidence was calculated only from affected carriers (figure). The clinical spectrum of disease includes asymmetry at symptom onset and a favorable response to levodopa therapy. Nonmotor symptoms included hallucinations, depression, anxiety, cognitive impairment, and pain, as frequently reported in sporadic PD (table). The most common initial symptom in Lrrk2 p.R1441C patients was rest tremor (57%), followed by bradykinesia (18%) and mixed motor symptoms (18%). One patient was reported to have dementia and four additional patients had mild cognitive impairment; there were no data on the cognitive status in 6 of the 33 affected Lrrk2 p.R1441C carriers. There were insufficient data on Lrrk2 p.R1441C carriers who did not have evidence for parkinsonism to comment on possible nonmotor complications.

Pathology findings have previously been reported for four Lrrk2 p.R1441C carriers from Family D (Western Nebraska).[22] Lewy body disease (LBD) was found in two patients but the pathologic spectrum also included pure dopaminergic cell loss in the substantia nigra (n = 1) without distinctive pathology and tau pathology (n = 1) (table).[2]

Genotyping of Lrrk2 p.R1441C carriers from 20 families revealed two major haplotypes for which gametic phase could be established, of four classes in total (figure e-1). The first haplotype class was identified in all Italian patients, as well as in German, Spanish, and American patients. The second haplotype was present in all Belgian families and the American Family D (Western Nebraska). This indicates a minimum of two independent founders.[9,14] A German and an Irish patient shared a third haplotype for which phase could

not be determined. In addition, the proband from Singapore carried alleles that could not be assigned to any of the other haplotype classes. Genetic analysis employing PHASE v2.1.1 estimates that the two haplotypes most commonly found in *LRRK2* c.4321C>T (p.R1441C) mutation carriers each have a frequency of <1% in 80 control subjects. The allele frequencies in US control subjects were comparable with frequencies obtained from 300 Belgian control subjects (data not shown). The small number of carriers did not allow mutation age to be estimated from the size and genetic variability within each haplotype class.[4]

DISCUSSION

The present study examines clinical and genetic features of Lrrk2 p.R1441C substitution carriers from three continents. The clinical spectrum of Lrrk2 p.R1441C substitution carriers includes all four cardinal signs of PD (table). Furthermore, asymmetry at disease onset and a favorable response to levodopa therapy were frequently present as seen in sporadic PD.[23] A family history of parkinsonism was observed in most cases, and may be the only clinical feature that differentiates Lrrk2 p.R1441C substitution carriers from sporadic PD. Indeed, all cases examined herein would fulfill published criteria for a diagnosis of idiopathic PD.[17]

The age-specific cumulative incidence of PD in carriers of the Lrrk2 R1441C mutation is shown in the figure. Fewer than 20% of the mutation carriers showed PD symptoms before the age 50 years, while at age 75 years >90% of them had developed symptoms. Accurate penetrance estimates are crucial for proper genetic counseling. Our figures on the age-specific cumulative incidence of disease must be interpreted with caution as they may overestimate the risk for PD in p.R1441C mutation carriers. This is due to ascertainment bias as most carriers were identified in studies targeting series of large, multicase PD families (thereby biased toward high penetrance). The penetrance estimate for a given mutation may be lower if measured among carriers from unselected, consecutive series of patients (including familial and sporadic PD), even more so, in studies from population-based cohorts. The rarity of Lrrk2 p.R1441C makes prospective population studies difficult, although less biased penetrance estimates on Lrrk2 p.G2019S carriers, which are especially frequent in Ashkenazi and Berber-Arab peoples, may be feasible.[24,25]

Our genetic investigation of p.R1441C mutation carriers reveals evidence of several founders originating from different parts of the world (figure e-1).[20] Lrrk2 p.R1441C is evidently a hotspot for mutation events. Indeed, this peptide region appears especially susceptible as two other putatively pathogenic amino acid substitutions, p.R1441G and p.R1441H, affect the same residue, and a third, p.A1442P, is adjacent. These residues are normally highly conserved across species and even between the ancestral Lrk1 within invertebrates and Lrrk1 and Lrrk2 in vertebrate radiations.[26]

The present study highlights the clinical overlap between p.R1441C substitution carriers, p.G2019S carriers, and idiopathic PD, indicating that the effect of mutations in different domains of the Lrrk2 protein lead to similar phenotypes. It is hypothesized that *LRRK2* mutations cause PD through a dominant gain of function effect.[20] Lrrk2 p.G2019S appears to increase kinase activity in several studies but results are conflicting regarding the impact of other substitutions on Lrrk2 kinase activity, including p.R1441C located in the GTPase domain.[27] However, GTP binding to the Roc domain may be critical for Lrrk2 phosphorylation and subsequent kinase activation.[28–30] Lrrk2 mutations may exert their effects by interfering with the cellular and stoichiometric interaction of Lrrk2 with its binding partners or alter Lrrk2 cellular stability and localization.[27]

As for the Lrrk2 p.G2019S substitution, LBD may be the most frequent pathologic finding in p.R1441C carriers particularly in cases where no atypical signs are present (e.g., supranuclear palsy). The pathologic spectrum can also include pure dopaminergic cell loss in the substantia nigra without distinctive pathology and tau pathology.[2] These findings highlight that the clinical syndrome referred to as PD may be present in the absence of LBD.

The discovery of *LRRK2* mutations in clinically typical, late-onset PD provides an unprecedented opportunity to advance our knowledge regarding the molecular mechanisms defining the disease and to develop better animal models for initial compound screening. Prospective studies may further elucidate the clinical course of Lrrk2 parkinsonism. Genetic testing may not be warranted in routine clinical practice; however, it is crucial for further research. Asymptomatic mutation carriers will provide insight into the preclinical disease course, facilitate biomarker development, and may be the first to benefit from neuroprotective treatment aimed at halting disease progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY

COR	C-terminal of Roc
GTPase	guanosine triphosphatase
LBD	Lewy body disease
PD	Parkinson disease
SNPs	single nucleotide polymorphisms

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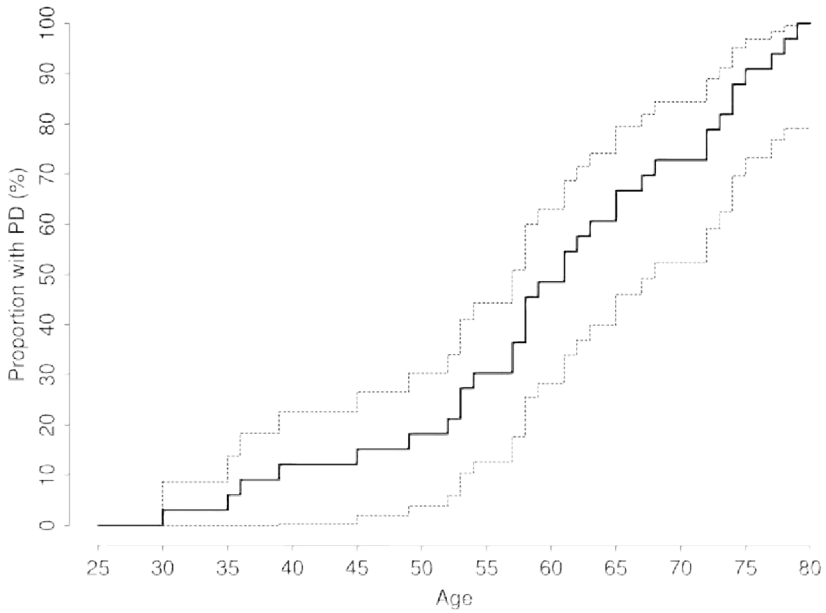

Figure. Cumulative incidence of PD in affected carriers

Kaplan-Meier curve of age-specific cumulative incidence of Parkinson disease (PD) calculated from 33 affected Lrrk2 p.R1441C substitution carriers, including the 95% CIs (dotted).

Table

Clinical and pathologic features in *LRRK2* c.4321C>T (p.R1441C) mutation carriers

Features	Values
Mean ± SD age in affected carriers, y; range (n)*	68 ± 10; 50–85 (33)
Mean ± SD age in unaffected carriers, y; range (n)†	62 ± 14; 33–84 (15)
Mean ± SD age at onset, y; range	60 ± 13; 30–79
Mean ± SD Unified Parkinson Disease Rating Scale III; range	19 ± 11; 6.5–42
Mean ± SD Hoehn & Yahr staging; range	2.5 ± 0.8; 1.5–5
Asymmetry (n)‡	Present (17)
Levodopa response (n)§	Favorable (25)
Familial/sporadic Parkinson disease, n	29/4
Additional symptoms (n)	Depression (9), fluctuations (10), anxiety (6), mild cognitive impairment (4), dementia (1), hallucinations (2)
Pathologic features (n)	Nigral degeneration in all (4), Lewy bodies in brainstem (1), widespread Lewy body disease(1), tau deposits (1)

Data from the last neurologic examination; however, the presence of asymmetry was recorded at the initial examination. Pathology findings are presented in references 2 and 22.

*Includes living mutation carriers.

†Includes deceased individuals and three obligate mutation carriers.

‡No asymmetry was found in three patients and no data were available in 13 patients.

§Two had no response to levodopa; data are not available on six patients.