Increased Stroke Risk in Patients with Parkinson's Disease with *LRRK2* Mutations

Parkinson's disease (PD) is associated with an increased stroke risk, however, no relationship between coronary artery disease (CAD) and PD was found.[1] To date, little is known about the influence of PD-related genes, such as the leucine-rich repeat kinase 2 (*LRRK2*), the parkin (*PRKN*) and the glucocerebrosidase (*GBA*) genes, in the vascular risk of these patients. This work aims to determine whether the vascular risk differs between sporadic/familial PD forms and controls.

We recruited 355 patients with sporadic PD (sPD), 38 with *GBA*-associated PD (*GBA*-PD), 36 with *LRRK2*-associated PD (*LRRK2*-PD), and 23 with *PRKN*-associated PD (*PRKN*-PD) and 620 controls. Demographic, clinical, and vascular risk factors data were collected. The presence of vascular events (ischemic stroke and CAD) were determined by clinical interview and consulting electronic medical records. We applied multivariate logistic regression and Cox regression analyses. In a confirmatory analysis, we repeated our multivariate analysis only with subjects who had a neuroimaging test (computed tomography or magnetic resonance imaging) available in their electronic records. The mutational screening of *PRKN*, *GBA*, and *LRRK2* genes was previously performed using a combination of high-resolution melting and direct DNA resequencing (Appendix S1).[2,3]

Patients with sPD were significantly older than controls and patients with *GBA*-PD. Patients with *PRKN*-PD had a lower rate of arterial hypertension. There were no other differences in vascular risk factors among the groups (Table S1). *PRKN*-PD showed a significantly younger PD onset and longer disease duration than the other groups, and *GBA*-PD had a younger disease onset than sPD (Tables S4–S6). However, there were no differences in other PD features.

The prevalence of ischemic stroke differed among groups, and this difference was statistically significant after controlling for sex, age, and vascular risk factors (Tables S7 and S8). However, no differences in CAD were found among groups. *LRRK2*-PD had the highest proportion of stroke (13.8%), followed by *PRKN*-PD and sPD (8.6% and 5.6%, respectively). *LRRK2*-PD showed a significantly increased risk of stroke compared with controls (odds ratio [OR], 5.1; 95% confidence interval [CI], 1.7–15.3; $P = 0.004$), whereas there were no significant differences in the other PD cohorts (Fig. 1A). In our confirmatory analysis, we corroborated the previous finding. Interestingly, in this analysis sPD also showed a marginally significant increased risk of stroke compared with controls (OR, 1.8; 95% CI, 0.99–3.2; $P = 0.05$; Fig. 1B). There was a statistically significant difference in the survival distribution for ischemic stroke among groups (Fig. 1C). The increased risk of stroke in *LRRK2*-PD was associated with a younger age at stroke compared with controls, a finding supported by our confirmatory analysis (Fig. 1D).

Our results are aligned with previous studies.[4,5] A meta-analysis concluded that the overall PD group had a 1.7-fold increase in the risk of stroke compared with controls, without differences in CAD.[1] In our study, sPD showed a similar increase in the stroke risk, although this association was marginally significant. *LRRK2*-PD showed a 5.1-fold increase in the risk of ischemic stroke after controlling for potential confounding factors. These results might be related to a different pathophysiology of stroke in certain PD subtypes compared with controls. A link between these brain disorders has been proposed, beyond the classical risk factors, considering the role of oxidative stress, neuroinflammation, and altered lipid metabolism among others.[6] Interestingly, it has been suggested that pathogenic variants of *LRRK2* might contribute to postischemic brain damage and neuroinflammation.[7]

In conclusion, patients with *LRRK2*-PD may show an increased risk of ischemic stroke, with no differences in CAD. The sporadic forms of PD might have a higher cerebrovascular risk than controls. Conversely, patients with *GBA*-PD and *PRKN*-PD showed a similar vascular risk to controls. Our results support the idea that mechanisms other than classical vascular risk factors might be involved in the cerebrovascular disease of those patients. Prospective studies are needed to confirm these findings.

Detailed introduction, methods, results, and discussion are included in Appendix S1.

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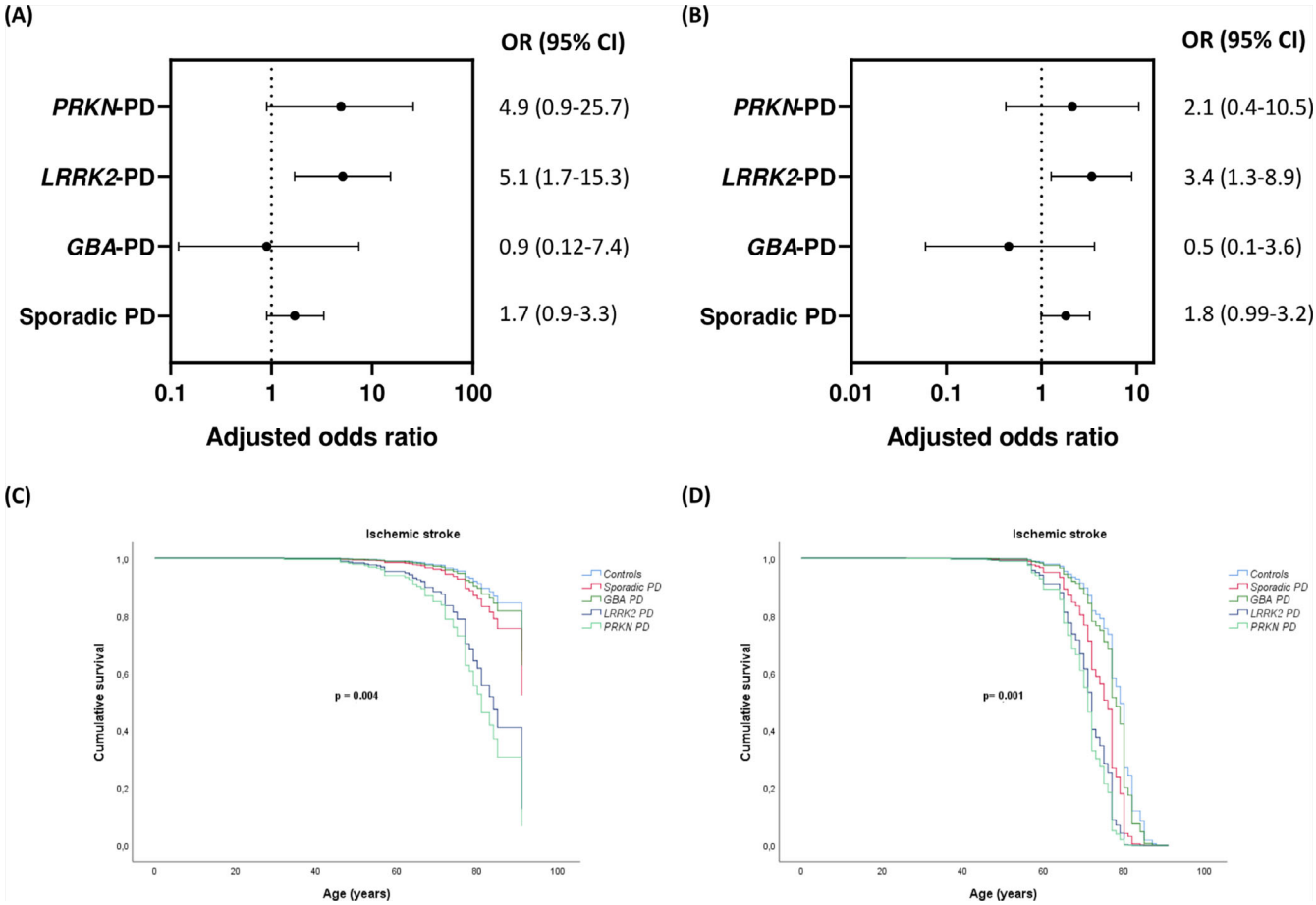

FIG. 1. Multivariate logistic regression and Cox regression model to determine the association between the occurrence of ischemic stroke and the study groups. (**A**) Forest plot with adjusted odds ratio and confidence intervals of symptomatic ischemic stroke within the disease groups compared with controls. (**B**) Forest plot with adjusted odds ratio and confidence intervals of neuroimaging-confirmed ischemic stroke within the disease groups compared with controls. (**C**) Survival plots of symptomatic ischemic stroke in the Parkinson's disease groups and controls. Lines represent the cumulative event-free survival in years of age. (**D**) Survival plots of neuroimaging-confirmed ischemic stroke in the Parkinson's disease groups and controls. Lines represent the cumulative event-free survival in years of age. CI, confidence interval; *GBA*-PD, patients with *GBA*-associated Parkinson's disease; *LRRK2*-PD, patients with *LRRK2*-associated Parkinson's disease; OR, odds ratio; *PRKN*-PD, patients with *PRKN*-associated Parkinson's disease; sPD, patients with sporadic Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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Supplementary Material

Supplementary introduction

Parkinson's disease (PD) is the most prevalent neurodegenerative disorder, after Alzheimer's disease.[1] Although the pathological hallmarks of the disease (Lewy pathology, α-synuclein accumulation, midbrain dopaminergic cell degeneration) are well-known, the etiopathogenesis of PD remains unclear.[2–4] A multifactorial model has been proposed in which genetic and environmental factors modulate the risk of developing PD.[3] Several authors have stated that a different approach is needed, considering that PD is not a single disease but various entities that converge in dopaminergic cell degeneration.[4] Numerous epidemiological and observational studies have linked vascular events with PD,[5–13] with a number of studies describing the influence of stroke and myocardial infarction on mortality among PD and other parkinsonian syndromes, sometimes with controversial results.[5–7] Other studies have attempted to clarify whether PD is a risk factor for developing a vascular event. Whereas a number of authors have found no differences between patients with PD and controls in terms of cumulative stroke incidence or have found a reduced risk of stroke among patients with PD,[8,9] other studies have reported an increased risk of stroke in PD.[10–13] Regarding coronary artery disease (CAD) in PD, studies with large cohorts have shown controversial results.[10,13,14] A prospective study in a Taiwanese population showed an increased risk of acute myocardial infarction in patients with PD, while a European epidemiological study reported no differences between PD and controls in the proportion of CAD.[10,14] A recent meta-analysis concluded that PD is associated with an increased risk of stroke.[15] Nevertheless, the authors found no relationship between PD diagnosis and CAD or cardiovascular mortality. Malek et al. reported an association between cerebrovascular disease and motor/cognitive features in patients with recently diagnosed PD.[16] It has been suggested that aspects other than the classical risk factors might influence the link between PD and vascular disease (e.g., altered glucose and lipid metabolism, oxidative stress, and neuroinflammation).[17] A number of studies have proposed a possible cardioprotective effect of various proteins related to PD etiology (such as Parkin, DJ-1, and PINK1), whereas other studies have suggested that the leucine-rich repeat kinase 2 (*LRRK2)* gene could contribute to post-ischemic neural damage and neuroinflammation.[18–20] Furthermore, a genome-wide association study showed that certain genes were shared between ischemic stroke and PD,[21] supporting the idea of common molecular pathways between the two diseases. Pathogenic variants in *LRRK2, Parkin* (*PRKN)* and glucocerebrosidase (*GBA*) genes are considered the main genetic factors that predispose individuals to the development of PD.[3] Various studies have described the specific clinical phenotypes of these patients.[22,23] Other specific clinical features have been shown in the familial forms of PD; for instance, an increase in certain types of cancer among patients with *LRRK2* mutations compared with idiopathic PD.[24] Surprisingly, survival studies among familial and sporadic forms of PD have shown controversial results, suggesting that other factors might play a role in their survival.[25,26] Finally, a specific serum lipid profile was described in a statin-free study in PD patients with *GBA* mutations compared with other forms of PD.[27] To date, little is known about the influence of PD-related genes in vascular disease. Given the reported

association between cerebrovascular events and PD, the present study is aimed at determining whether the vascular risk differs between sporadic and familial forms of PD.

Supplementary Methods

Participants

We conducted this study with patients with PD recruited from the Movement Disorder Clinic at Hospital Universitario Virgen del Rocio in Seville, Spain. PD was diagnosed following the Movement Disorder Society Clinical Diagnostic Criteria.[28] We recruited controls from the same geographical area and did not include those who had any neurodegenerative disorder, a family history of PD or a pathogenic variant in *PRKN, GBA* or *LRRK2.* Patients with PD with known mutations in PD-related genes other than *PRKN, GBA* or *LRRK2* were neither included in the study. We classified the patients with PD based on their genetic status: patients with *LRRK2*-associated PD (*LRRK2*-PD), patients with *GBA*-associated PD (*GBA*-PD), patients with *PRKN*-associated PD (*PRKN*-PD) and patients with sporadic PD (sPD). All genetic variants were classified in accordance with the American Society of Human Genetics guidelines. All the individuals considered for the study were Caucasian to avoid ethnic influences. We included a total of 1108 individuals and divided them into 5 groups: 362 sPD, 38 *GBA*-PD, 36 *LRRK2*-PD, 23 *PRKN*-PD and 649 controls (Figure S1).

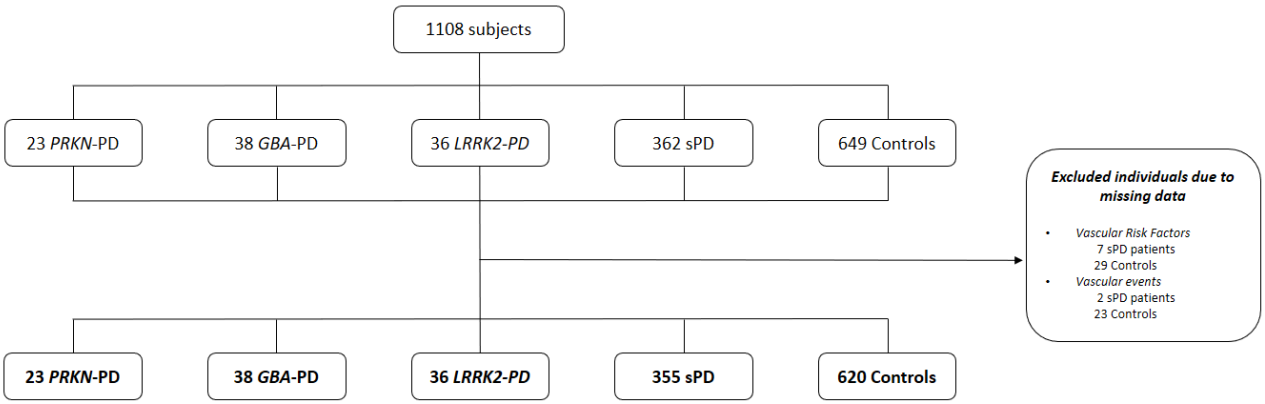

Figure S1. Flowchart for the distribution of the study participants. Resulting groups are represented in bold. sPD, patients with sporadic Parkinson's disease; *LRRK2*-PD, patients with *LRRK2*-associated Parkinson's disease; *GBA*-PD, patients with *GBA*-associated Parkinson's disease; *PRKN*-PD, patients with *PRKN*-associated Parkinson's disease.

None of the individuals included in the study were blood relatives. All participants underwent a clinical assessment at our centre, and we retrospectively obtained their demographic data by reviewing their electronic medical records. Serum creatinine levels were determined in peripheral blood and analyzed in the central laboratory of our center. The presence of vascular risk factors (arterial hypertension, diabetes, hyperlipidemia, and smoking habit) and vascular events (ischemic stroke and CAD) were determined in our cohort during the clinical interview and by consulting electronic medical records. Regarding the diagnosis of symptomatic cerebrovascular events, patients should have been

diagnosed by a neurologist and events should have been confirmed by the presence of radiological findings (cerebral infarct) on brain imaging (computed tomography, CT, or magnetic resonance imaging, MRI). We classified the various types of ischemic strokes, following the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, into 4 separate categories: lacunar infarct, atherothrombotic, cardioembolic and cryptogenic.[29] We also added the category transient ischemic attack (TIA). All types of symptomatic CAD were considered, and patients should have been diagnosed by a cardiologist.
We retrospectively reviewed all the neuroimaging tests (brain CT or MRI) available in the subjects' electronic records (PD patients and controls). For the neuroimaging-confirmed analyses, we considered as a positive finding both: a) symptomatic strokes confirmed by a neuroimaging test; and b) asymptomatic strokes diagnosed by a neuroimaging test conducted for other reasons. White matter hyperintensities were not considered for the analysis. In the confirmatory analysis, the resultant cohorts were: 267 controls, 257 sPD, 33 *GBA*-PD, 34 *LRRK2*-PD and 21 *PRKN*-PD.

The study was approved by the ethics committee of the University Hospital Virgen del Rocio, and we obtained written informed consent from all the participants in the study.

Genetics

We isolated genomic DNA from peripheral blood samples by standard or automated methods (DNA Isolation Kit for Mammalian Blood, Roche; MagNA Pure LC, Roche Diagnostics, Indianapolis, IN, USA), in compliance with established protocols.

GBA screening

Polymerase chain reaction (PCR) primer couples were designed on the basis of the known genomic sequence (NG_009783.1). To prevent amplification of the neighbouring pseudogene, *GBA* was first amplified in 4 large fragments that only and specifically amplified the functional gene but not the nearby pseudogene. For the mutational screening, we studied isoform 1 of the *GBA gene* (NM_001005741. 2), which contains 12 exons, including a noncoding exon 1. The mutational screening of all exons and intron-exon boundaries was then performed, using a combination of high-resolution melting (HRM) analysis and direct DNA resequencing. HRM reactions were performed on a LightCycler480 (LC480) instrument, and HRM curve acquisition and analysis were performed using LC480 software version 1.3 (Roche Applied Science, Indianapolis, IN, USA). Samples showing abnormal melting profiles, including those with variants, were sequenced on both strands using the BigDye terminator cycle sequencing kit (Applied Biosystems, Foster City, CA, USA) and resolved on an ABI3500 genetic analyzer (Applied Biosystems).
We have adopted the conventional nomenclature, which refers to the processed protein and excludes the 39-residue signal peptide.

LRRK2 screening

The mutational screening of all exons and intron-exon boundaries was performed using a HRM analysis and/or targeted resequencing. HRM reactions were performed on a LightCycler480 (LC480) instrument, and HRM curve acquisition and analysis were

performed using LC480 software version 1.3 (Roche Applied Science). All samples showing abnormal melting profiles were sequenced by Sanger sequencing.
Targeted resequencing was performed using a customized Haloplex Target Enrichment Panel (including *LRRK2*), which was designed using Agilent's online Sure Design tool, following the manufacturer's protocol (Agilent Technologies, Inc., Santa Clara, CA, USA). Additionally, an extension of the first panel was designed using a customized KAPA target Enrichment Panel, which was designed using Roche's online HyperDesign tool, following the manufacturer's protocol (Roche Diagnostics). Samples were sequenced employing the Illumina NextSeq platform (Illumina Inc., San Diego, CA, USA). Reads were mapped against the hg38 reference genome by using the Burrow-Wheeler Aligner (BWA). Variant calling was obtained using an in-house pipeline which takes advantage of the GATK Best Practices workflow. Produced VCFs were processed with eVAI software (enGenome; https://evai.engenome.com/#login) for annotation. Filtered variants predicted as pathogenic were validated by Sanger sequencing.

PRKN screening

Mutations in *PRKN* were screened in all subjects using HRM as well as targeted sequencing as described before. CNV was analysed using data from targeted sequencing as well as MLPA analysis.

Statistical analysis

We performed group comparisons of the categorical variables using the chi-squared test or Fisher's exact test, as appropriate. We employed an analysis of variance (ANOVA) for comparisons of means and applied post hoc tests when necessary. We applied logistic regression models to determine the association between ischemic stroke or CAD and the study groups, adjusting for potential confounding factors (sex, age, and vascular risk factors). If an association was found, we used odds ratios (OR) to examine the risk of a vascular event (ischemic stroke or CAD) among the various cohorts of PD compared with the controls. We employed Cox regression analysis to examine the association between the study groups and the occurrence of a vascular event (ischemic stroke or CAD) as a time-dependent outcome, censoring at age during the last follow-up or age at death. To avoid potential bias regarding stroke overdiagnosis in the PD population, we reviewed all neuroimaging studies (CT or MRI) available in the subjects' records conducted for any other reason. In a confirmatory analysis, we repeated our multivariate analysis (logistic multivariate regression and Cox regression) only with subjects who had a neuroimaging test. We performed all the statistical analyses with IBM SPSS software (26 for Windows; IBM, Armonk, NY, USA) and the R studio software package. A p-value < 0.05 was considered statistically significant.

Supplementary results

Participant clinical and demographic characteristics

Figure 1 shows the final study groups. Table S1 lists the demographic and clinical characteristics of the study groups. The *LRRK2*-PD group consisted on 29 *LRRK2* p.G2019S PD patients (80.6 %) and 7 *LRRK2* p.R1441G PD patients (19.4%). The list of

GBA pathogenic variants considered for the inclusion of patients in the *GBA*-PD group is shown in Table S2, the most frequent variant being p.N370S (34% of *GBA*-PD). The *PRKN*-PD group contained 15 PD patients with homozygous mutations in *PRKN* (65.2%) and 8 PD patients with compound-heterozygous mutations in *PRKN* (34.8%). The most frequent pathogenic variant was the *PRKN* frameshift variant p.Asn52fs, c.155delA (43% of *PRKN*-PD). The list of *PRKN* pathogenic variants considered for the inclusion in the *PRKN*-PD group is shown in Table S3.

Table S1. Demographic and clinical data of the controls and Parkinson's disease groups

	sPD (n= 355)	***GBA*-PD (n=38)**	***LRRK2*-PD (n=36)**	***PRKN*-PD (n=23)**	**Controls (n= 620)**	***p-value***
Sex, n male (% male)	218 (61%)	24 (63%)	14 (39%)	14 (61%)	334 (54%)	0.04 †
Age, years ± SD	65.76 ± 11.42	59.74 ± 10.89	63.53 ± 12.01	56.61 ± 15.59	59.35 ± 16.1	< 0.05 §
Arterial hypertension, n(%)	153 (43%)	19 (50%)	18 (50%)	3 (13%)	276 (45%)	0.04 †
Diabetes, n (%)	62 (18%)	5 (13%)	7 (19%)	2 (9%)	117 (19%)	0.66 †
Hyperlipidemia, n (%)	89 (25%)	9 (23%)	13 (36%)	6 (26%)	193 (31%)	0.24 †
Smoking habit, n (%)	108 (30%)	12 (32%)	13 (36%)	11 (48%)	219 (35%)	0.42 †
Serum creatinine (mg/dl), mean ± SD	0.88 ± 0.53	0.84 ± 0.14	0.80 ± 0.18	0.75 ± 0.18	0.95 ± 0.72	0.21 §
Age at disease onset, years ± SD	56.32 ± 11.84	49.18 ± 9.98	52.23 ± 12.61	33.09 ± 11.19	-	< 0.05 §
Disease duration, years ± SD	8.91 ± 6.13	10.72 ± 7.64	11.10 ± 6.73	22.83 ± 11.36	-	< 0.05 §
Hoehn & Yahr, mean ± SD	2.22 ± 1.42	2.46 ± 0.91	2.01 ± 2.10	2.43 ± 0.88	-	0.54 §
LEDD, mean ± SD	745.18 ± 451.32	648.04 ± 407.86	887.63 ± 651.78	703.46 ± 471.34	-	0.20 §

LEDD, levodopa equivalent daily dose; sPD, sporadic Parkinson's Disease; *GBA*-PD, patients with *GBA*-associated PD; *LRRK2*-PD, patients with *LRRK2*-associated PD; *PRKN*-PD, patients with *PRKN*-associated PD. Data are presented as means ± standard deviation (SD) or number (n) with percentage (%). §, analysis of variance (ANOVA); †, chi-squared test.

Table S2. The list of *GBA* pathogenic variants considered for the inclusion of patients in *GBA*-PD group.

Allele	cDNA	Protein	Exon	n
D409H	c.1342G/C	p.Asp448His	10	2
L444P	c.1448T/C	p.Leu483Pro	11	4
N370S	c.1223A/G	p.Asn409Ser	10	13
S310G	c.928A/G	p.Ser310Gly	8	3
L29fs	c.84dupG	p.Leu29Alafs*18	3	1
R535H	c.1604G>A	p.Arg535His	12	1
V457D	c.1487T/A	p.Val496Asp	11	2
G195W	c.700G>T	p.Gly234Trp	7	1
F213I	c.754T>A	p.Phe252Ile	7	2
R262C	c.901C>T	p.Arg301Cys	8	1
E326K	c.1093G>A	p.Glu365Lys	9	8

Table S3. The list of *PRKN*-PD patient with the cigosity and mutation found in each patient

***PRKN*-PD patient**	**Cigosity**	**Mutation**
1	Homozygous	p.Asn52fs; c.155delA
2	Homozygous	p.Gly430Ser; c.1288 G>A
3	Homozygous	p.Trp74fs; c.220_221dupTG
4	Homozygous	Complete deletion of exon 3 in heterozigosity and complete deletion of exon 4 in homozygosity
5	Homozygous	Complete deletion of exon 5 and 6
6	Homozygous	p.Trp74fs; c.220_221dupTG
7	Compound heterozygous	p.Asn52fs; c.155delA Complete deletion of exon 3 and 4
8	Homozygous	p.Asn52fs; c.155delA
9	Homozygous	p.Asn52fs; c.155delA
10	Compound heterozygous	p.Trp74fs; c.220_221dupTG Complete deletion in exon 8 and 9
11	Homozygous	p.Trp74fs; c.220_221dupTG
12	Homozygous	p.Asn52fs; c.155delA
13	Compound heterozygous	p.Arg275Trp, c.823C>T Complete deletion of exon 3 and 4
14	Homozygous	p.Thr415Asn; c.1244C>A
15	Compound heterozygous	p.Asn52fs; c.155delA c.1286-2A>T
16	Homozygous	p.Asn52fs; c.155delA
17	Compound heterozygous	p.Thr415Asn; c.1244C>A p.Asn52fs; c.155delA
18	Homozygous	p.Arg275Trp","c.823C>T
19	Compound heterozygous	p.Asn52fs; c.155delA Complete deletion of exon 5 and 6
20	Compound heterozygous	p.Trp74fs, c.220_221dupTG c.1286-3C>G
21	Homozygous	p.Trp74fs, c.220_221dupTG
22	Compound heterozygous	Complete deletion in exon 8 and 9 Complete deletion in exon 3 and 4
23	Homozygous	p.Asn52fs; c.155delA

There were statistically significant differences among groups in terms of age. The post hoc test applied to study age among the groups showed that sPD patients were significantly older than controls and *GBA*-PD patients (Table S4). However, there were no statistical differences in age between either familial PD groups and controls or between the *LRRK2*-

PD group and the sPD. *LRRK2*-PD had a female predominance (61%), whereas the *GBA*-PD, sPD, *PRKN*-PD, and controls had a male predominance (63%, 61%, 61% and 54%, respectively). In comparison to other groups, *PRKN*-PD had a lower rate of arterial hypertension. However, there were no other differences in vascular risk factors or serum creatinine levels between the groups (Table S1). *PRKN*-PD patients showed a significantly younger onset of PD than the other PD groups, and *GBA*-PD had a younger onset of disease than sporadic PD. There were no differences between *LRRK2*-PD and either sporadic or *GBA*-PD (Table S5). There were statistically significant differences in disease duration between the *PRKN*-PD group and the other PD groups (Table S6). However, there were no differences in terms of dopaminergic treatment (levodopa equivalent daily dose) or disease severity (Hoehn & Yahr scale) among groups.

Table S4. Games-Howell post hoc comparisons for age among study groups

		95% CI for Mean Difference					
Comparison	**Mean Difference**	**Lower**	**Upper**	**SE**	**t**	**Df**	**P value**
Controls - sPD	-6.414	-8.838	-3.990	0.887	-7.233	929.803	< 0.01 **
Controls - *GBA*	-0.388	-5.723	4.947	1.882	-0.206	47.559	1.000
Controls -*LRRK2*	-4.179	-10.168	1.811	2.103	-1.987	42.691	0.290
Controls -*PRKN*	2.740	-7.037	12.518	3.317	0.826	23.778	0.920
sPD - *GBA*	6.027	0.724	11.329	1.868	3.226	46.146	0.019 *
sPD - *LRRK2*	2.236	-3.725	8.196	2.091	1.069	41.677	0.821
sPD - *PRKN*	9.155	-0.607	18.916	3.309	2.767	23.551	0.073
GBA - LRRK2	-3.791	-11.265	3.683	2.669	-1.420	70.382	0.617
GBA - PRKN	3.128	-7.513	13.769	3.702	0.845	35.083	0.915
LRRK2 - PRKN	6.919	-4.010	17.848	3.819	1.812	38.350	0.382

* p < 0.05, ** p < 0.01. sPD, sporadic Parkinson's disease; *GBA*, patients with *GBA*-associated PD; *LRRK2*, patients with *LRRK2*-associated PD; *PRKN*, patients with *PRKN*-associated PD.

Table S5. Tukey post hoc comparisons for age at disease onset among study groups

		95% CI for Mean Difference				
Comparison	**Mean Difference**	**Lower**	**Upper**	**SE**	**t**	**P value**
sPD - *GBA*	7.137	1.972	12.301	2.003	3.564	< 0.01**
sPD - *LRRK2*	4.092	-1.268	9.453	2.079	1.969	0.20
sPD - *PRKN*	23.234	16.725	29.743	2.524	9.205	< 0.01**
GBA - LRRK2	-3.044	-10.130	4.041	2.748	-1.108	0.69
GBA - PRKN	16.097	8.107	24.087	3.098	5.195	< 0.01**
LRRK2- PRKN	19.142	11.023	27.260	3.148	6.080	< 0.01**

** p < 0.01. sPD, sporadic Parkinson's disease; *GBA*, patients with *GBA*-associated PD; *LRRK2*, patients with *LRRK2*-associated PD. *PRKN*, patients with *PRKN*-associated PD. P-value and confidence intervals adjusted for comparing a family of 3 estimates (confidence intervals corrected using the tukey method).

Table S6. Games-Howell post hoc comparisons for disease duration among PD groups

		95% CI for Mean Difference					
Comparison	**Mean Difference**	**Lower**	**Upper**	**SE**	**t**	**Df**	**P value**
sPD - *GBA*	-1.807	-5.394	1.780	1.337	-1.352	39.069	0.54
sPD - *LRRK2*	-2.260	-5.406	0.886	1.176	-1.921	41.951	0.24
sPD - *PRKN*	-13.919	-20.531	-7.307	2.389	-5.826	22.958	< 0.01**
GBA - LRRK2	-0.452	-4.961	4.056	1.711	-0.264	67.435	0.99
GBA - PRKN	-12.112	-19.375	-4.849	2.693	-4.497	35.062	< 0.01**
LRRK2- PRKN	-11.659	-18.750	-4.569	2.617	-4.455	32.038	< 0.01 **

** p < 0.01. sPD, sporadic Parkinson's disease; *GBA*, patients with *GBA*-associated PD; *LRRK2*, patients with *LRRK2*-associated PD. *PRKN*, patients with *PRKN*-associated PD.

Multivariate logistic regression models assessing the risk of stroke and CAD

The prevalence of ischemic stroke differed among the groups, and this difference was statistically significant after controlling for sex, age, and vascular risk factors (Table S6). Intergroup comparisons showed that the prevalence of ischemic stroke in the *LRRK2*-PD group was significantly higher after adjusting for potential confounders (Table S7). All the *LRRK2*-PD patients with stroke carried the p.G2019S mutation. Although the prevalence of CAD in the *PRKN*-PD group was slightly lower than in the others, this difference was not significant (Table S6).

Table S7. Prevalence and characteristics of vascular events (ischemic stroke and coronary artery disease) in Parkinson's disease groups and controls

	sPD (n= 355)	***GBA*-PD (n=38)**	***LRRK2*-PD (n=36)**	***PRKN*-PD (n=23)**	**Controls (n= 620)**	***p-value***
Ischaemic stroke, n (%)	20 (5.6%)	1 (2.6%)	5 (13.8%)	2 (8.6%)	21 (3.4%)	0.02*
Age at stroke, years mean ± SD	66.1 ± 12.2	48	61.8 ± 15.2	73.0 ± 8.5	70.1 ± 12.3	0.47§
NIHSS, mean ± SD	9.7 ± 6.3	2	3.0 ± 2	4.0 ± 2.8	2.2 ± 1.6	0.39†
Type of stroke, n						
TIA	*1*	*1*	*0*	*0*	2	-
Lacunar	*13*	-	*3*	*1*	5	-
Atherothrombotic	*1*	-	*0*	*0*	5	-
Cardioembolic	*4*	-	*0*	*0*	5	-
Cryptogenic	*1*	-	*2*	*1*	4	-
CAD, n (%)	21 (5.9%)	2 (5.3%)	4 (10.8%)	1 (4.3%)	48 (7.8%)	0.83*
Age at CAD, years mean ± SD	67.7 ± 10.3	51.5 ±4.9	62.3 ± 3.2	68	69.2 ± 10.5	0.08§

sPD, sporadic Parkinson's disease; *GBA*-PD, patients with *GBA*-associated PD; *LRRK2*-PD, patients with *LRRK2*-associated PD; *PRKN*-PD, patients with *PRKN*-associated PD; CAD, coronary artery disease; TIA, transient ischaemic attack; NIHSS, National Institutes of Health Stroke Scale. *Logistic regression model adjusted by sex, age and vascular risk factors. §, analysis of variance (ANOVA). †, Welch's test

Table S8. Multivariate logistic regression model comparing ischemic stroke prevalence among the different Parkinson's disease groups and controls.

	B	**Standard error**	**Wald**	**df**	**p-value**	**OR**	**95% CI**	
							Lower	**Upper**
Study group			10.33	4	0.02*	-	-	-
sPD	0.51	0.34	2.33	1	0.10	1.7	0.90	3.32
***GBA*-PD**	-0.06	1.05	0.00	1	0.95	0.9	0.12	7.36
***LRRK2*-PD**	1.57	0.56	7.96	1	0.004**	5.1	1.70	15.30
***PRKN*-PD**	1.39	0.83	2.86	1	0.07	4.9	0.94	25.71

* $p < 0.05$; ** $p < 0.01$. Logistic regression model adjusted for age, sex and vascular risk factors. CI, confidence interval; sPD, sporadic Parkinson's disease; *GBA*-PD, patients with *GBA*-associated PD; *LRRK2*-PD, patients with *LRRK2*-associated PD; *PRKN*-PD, patients with *PRKN*-associated PD.

No differences in terms of the age at stroke or the clinical severity of stroke were observed among the groups. When we classified the various types of ischemic stroke, we observed a predominance of lacunar infarction in the *LRRK2*-PD and sPD groups. Although no

differences in age at CAD were observed, the controls showed the highest age at the time of the cardiovascular event.

Cox regression analyses

We plotted survival curves for age at diagnosis of ischemic stroke and CAD for each cohort. There was a statistically significant difference in the survival distribution for ischemic stroke among the groups (Wald test 13.0, p = 0.011). Figure 1C shows that the increased risk for ischemic stroke in the patients with *LRRK2*-PD was associated with a younger age at stroke in that cohort. Patients with *PRKN*-PD also showed a different survival curve compared with controls. In our confirmatory analyses, the multivariate cox regression model confirmed the different survival curves for age at diagnosis of ischemic stroke of *LRRK2*-PD and *PRKN*-PD patients compared with controls (Figure 1D). Although PD patients showed lower age at CAD than controls, no significant differences were found in the survival distribution for CAD (Figure S2).

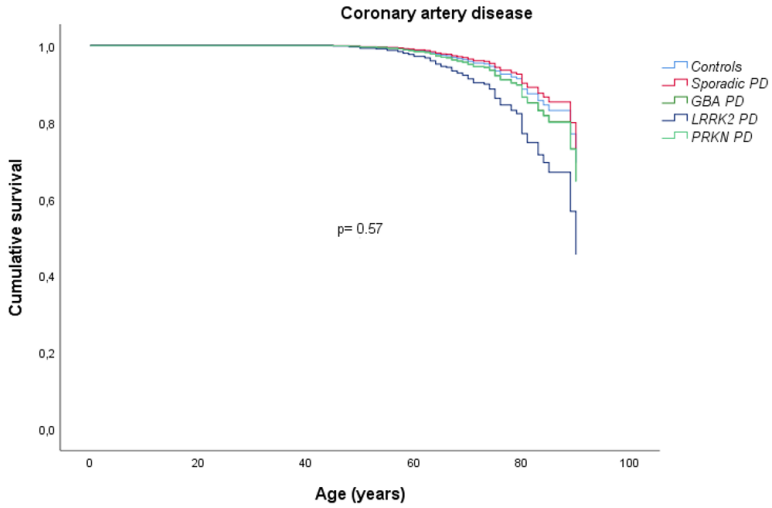

Figure S2. Survival plots of cardiovascular events in the Parkinson's disease groups and controls. Lines represent the cumulative event-free survival in years of age. sPD, patients with sporadic Parkinson's disease; *LRRK2*-PD, patients with *LRRK2*-associated Parkinson's disease; *GBA*-PD, patients with *GBA*-associated Parkinson's disease; *PRKN*-PD, patients with *PRKN*-associated Parkinson's disease.

Intragroup comparisons of subjects with and without stroke

Finally, we compared the characteristics of subjects with and without stroke within each group (Table S8). Controls and *PRKN*-PD patients who had a stroke were significantly older. *LRRK2*-PD and sPD who had a stroke were older, though this difference was not statistically significant. sPD patients and controls with stroke showed a significantly higher proportion of arterial hypertension and hyperlipidemia than sPD and controls without a stroke. Regarding the PD characteristics, there were no differences in terms of PD severity or dopaminergic treatment among those who had a stroke and those who did not. *PRKN*-PD patients who had a stroke showed a significantly longer disease duration than those who did not. In the other groups, however, there were no differences in disease duration. The age at disease onset in *LRRK2*-PD patients who experienced a stroke was significantly higher than in those who did not. The Hoehn & Yahr stage was higher in *PRKN*-PD patients who had a stroke than in those without it, and this difference was marginally significant.

Table S9. Intragroup comparison of subjects with and without stroke

	Sporadic PD (n= 355)			***GBA*-PD (n=38)**			***LRRK2*-PD (n=36)**			***PRKN*-PD (n=23)**			**Controls (n= 620)**		
Ischemic stroke	Yes	No	*p*	Yes	No	*p*	Yes	No	*p*	Yes	No	*p*	Yes	No	*p*
Sex, n male (% male)	12 (60%)	206 (62%)	0.89†	1 (100%)	23 (62%)	0.99‡	2 (40%)	13 (41%)	0.99‡	1 (50%)	13 (61%)	0.99‡	16 (71%)	319 (53%)	0.10†
Age, years ± SD	70.0 ± 10.3	65.5 ± 11.4	0.09§	51	59.97 ± 10.94	-	72.8±10.9	62.9 ± 11.8	0.06§	76.0 ± 8.5	54.7 ± 14.66	**0.05§**	69.9± 12.6	59.0 ± 16.1	**<0.01§**
Arterial hypertension, n(%)	17 (85%)	136 (41%)	**<0.01†**	0 (0%)	19 (51%)	0.99‡	4 (80%)	14 (45%)	0.34‡	1 (50%)	2 (10%)	0.25‡	16 (76%)	260 (43,5%)	**<0.01†**
Diabetes, n (%)	3 (15%)	59 (18%)	0.76†	0 (0%)	5 (13%)	0.99‡	1 (20%)	6 (19%)	0.99‡	1 (50%)	1 (5%)	0.17‡	6 (29%)	111 (19%)	0.248†
Hyperlipidemia, n (%)	9 (45%)	80 (24%)	**0.03†**	1 (100%)	8 (22%)	0.24‡	2 (40%)	11 (35%)	0.99‡	1 (50%)	5 (24%)	0.46‡	11 (52%)	182 (30%)	**0.03†**
Smoking habit, n (%)	7 (37%)	100 (30%)	0.55†	0 (0%)	12 (32%)	0.99‡	1 (20%)	12 (39%)	0.63‡	1 (50%)	10 (48%)	0.99‡	10 (48%)	209 (35%)	0.23†
Serum creatinine	0.96 ± 0.2	0.88 ± 0.5	0.56§	1.06	0.83 ± 0.14	-	0.76 ± 0.2	0.8 ± 0.2	0.71§	0.64 ± 0.18	0.76 ± 0.18	0.39§	1.14 ± 0.8	0.95 ± 0.7	0.41§
Age at PD onset, years ± SD	59.9 ± 12.4	56.1 ± 11.8	0.16§	46	49.3 ± 10.1	-	63.8 ± 10.9	50.3 ± 11.9	**0.02§**	33.0 ± 12.73	33.0 ± 10.8	0.99§			
Disease duration, years ± SD	9.2 ± 7.4	8.9 ± 6.1	0.85§	6	10.8 ± 7.7	-	8.2 ± 4.1	11.6 ±7.0	0.30§	40.5 ± 21.9	21.1 ± 9.1	**0.02§**			
Hoehn & Yahr, mean ± SD	2.3 ± 0.8	2.2 ± 1.4	0.83§	2	2.5 ± 0.9	-	2.6 ± 1.1	1.9 ± 2.3	0.26§	3.75 ± 1.8	2.3 ± 0.7	0.09§			
LEDD, mean ± SD	727.5 ± 265.7	746.2 ± 460.3	0.86§	775	659.6. ± 409.7	-	815.6 ± 539.5	899.6 ± 676.0	0.85§	576.5 ± 235.5	716.7 ± 489.7	0.96§			

LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; *GBA*-PD, patients with *GBA*-associated PD; *LRRK2*-PD, patients with *LRRK2*-associated PD; *PRKN*-PD, patients with *PRKN*-associated PD. Data are presented as means ± standard deviation (SD) or number (n) with percentage (%). §, analysis of variance (ANOVA) or Kruskal-Wallis test as appropriate; †, chi-squared test; ‡, Fisher's exact test. Bold values denote statistical significance at $p<0.05$

Supplementary discussion

Our study specifically described the diverse cerebrovascular and cardiovascular risk among patients with PD according to their genetic background, thereby helping to understand the possible link between stroke and PD etiology. Our main finding was that patients with *LRRK2*-PD showed an increased risk of ischemic stroke. These cerebrovascular events tended to occur at a younger age than in controls. However, no differences in CAD were found between the familial and sporadic forms of PD as well as controls.

The results of our study are aligned with those of previous studies.[10–12,15] Interestingly, in our confirmatory analysis, the increased risk of ischemic stroke in the sPD group compared with controls was marginally significant (adjusted OR 1.8; 95% CI 0.99-3.2; p=0.05). Although the *PRKN*-PD group also showed a non-significant increased risk of stroke, this finding was not confirmed in our confirmatory analysis. The *LRRK2*-PD group showed a 5.1-fold increase in the risk of ischemic stroke compared with controls. This increased risk seems to be particularly relevant in those *LRRK2*-PD patients who carried the p.G2019S mutation and with a late-onset disease. Although both sPD patients and controls who had a stroke showed higher rates of arterial hypertension and hyperlipidemia than those sPD patients and controls without stroke, there were no significantly differences in vascular risk factors within the *LRRK2*-PD group (Table S9). These results might be related to a different pathophysiology of stroke in some PD patients compared with controls.[19,20,30–32] Considering the role of *LRRK2* in neuroinflammation, a plausible explanation for the increased risk of stroke in our patients with *LRRK2*-PD could be related to a pro-inflammatory state that might contribute to small-vessel infarction.

A recent study showed higher triglyceride levels in *LRRK2*-PD compared with sPD with no relationship between metabolic syndrome and PD features.[33] In contrast, our group previously reported lower levels of serum lipoproteins and cholesterol in *GBA*-PD patients compared with controls and other PD forms in a statin-free study. Interestingly, there were no differences between *LRRK2*-PD patients and sPD or controls.[27] In our cohort, the proportion of hyperlipidemia was slightly lower in the *GBA*-PD group than in the other PD groups; however, no statistically significant differences were found between the groups (Table S1). Our results after conducting a multivariate analysis support the idea that mechanisms other than classical vascular risk factors might influence the described increased risk of stroke in PD.[15]

Regarding the type of stroke, we found that patients with sPD and those with *LRRK2*-PD showed a predominance of symptomatic lacunar infarction. These results are in line with a previous study in which no differences were found between patients with PD and controls, either in carotid artery arteriosclerosis or in the intima-media thickness.[34] Our confirmatory analysis also showed an increased stroke risk in *LRRK2*-PD and sPD compared with controls when both symptomatic and asymptomatic events were considered. In line with our results, Patel et al. reported that patients with PD showed an increased number of cerebrovascular disease events (both clinically and radiologically diagnosed) but showed no differences in vascular risk factors compared with controls.[11] In this study, however, a higher frequency of radiological small-vessel infarcts was reported in the controls compared with PD patients, as opposed to our findings. In contrast, a recent South Korean

nationwide study showed an increased risk of atrial fibrillation in PD, especially in those with an early age at disease onset.[35] Furthermore, *LRRK2* has been proposed as a possible gene related to atrial fibrillation maintenance.[36] Our main results do not support a possible link between cardioembolic stroke and PD, either in patients with sporadic or familial forms of PD.

No significant differences were found in CAD among the groups. As we mentioned above, these results are in line with previous studies, including a recent meta-analysis.[10,15] However, other studies with large cohorts have reported an increased risk of CAD in patients with PD.[13,14] These conflicting results could be explained by ethnic differences between the populations or different diagnostic criteria for the participants included in those studies.

Our study has limitations. First, the retrospective nature of our study requires our results to be interpreted cautiously, understanding their preliminary nature. Although we confirmed ischemic stroke with radiological findings, and vascular risk factors were included in our logistic model, certain factors out of our control (such as diet or statin doses) might have influenced our findings. Second, given that we did not consider asymptomatic *PRKN, GBA* or *LRRK2* carriers for the study, it was not possible to determine the risk of vascular events in these individuals. Further prospective studies within those populations would be necessary to determine the role of these genes in their vascular disease risk, regardless of PD neurodegeneration. Finally, our study was not designed to reach conclusions regarding cardiac abnormalities other than symptomatic myocardial infarction.

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