



HAL
open science

Differences in Survival across Monogenic Forms of Parkinson's Disease

Aymeric Lanore, Fanny Casse, Christelle Tesson, Thomas Courtin, Poornima Jayadev Menon, S. Sambin, Graziella Mangone, L.-L. Mariani, S. Lesage, Alexis Brice, et al.

► **To cite this version:**

Aymeric Lanore, Fanny Casse, Christelle Tesson, Thomas Courtin, Poornima Jayadev Menon, et al.. Differences in Survival across Monogenic Forms of Parkinson's Disease. *Annals of Neurology*, 2023, 94 (1), pp.123-132. 10.1002/ana.26636 . hal-04122825

HAL Id: hal-04122825

<https://hal.science/hal-04122825>

Submitted on 7 Jul 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.



L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Differences in Survival across Monogenic Forms of Parkinson's Disease

Aymeric Lanore, MD ,^{1,2} Fanny Casse, MSc,¹ Christelle Tesson, PhD,¹

Thomas Courtin, MD,^{1,3} Poornima Jayadev Menon, MD,^{1,2,4} Sara Sambin, MD, PhD ,^{1,2}
 Graziella Mangone, MD, PhD,^{1,2,5} Louise-Laure Mariani, MD, PhD,^{1,2} Suzanne Lesage, PhD,¹
 Alexis Brice, MD,^{1,3} Alexis Elbaz, MD, PhD ,⁶ and Jean-Christophe Corvol, MD, PhD,^{1,2†}
 for the French Clinicians Network for Parkinson's Disease Genetics (the PDG Group)

Objective: Survival of patients with monogenic Parkinson's disease may depend on the causative genes associated with the disease. In this study, we compare survival of patients with Parkinson's disease according to the presence of *SNCA*, *PRKN*, *LRRK2*, or *GBA* mutations.

Methods: Data from the French Parkinson Disease Genetics national multicenter cohort study were used. Patients with sporadic and familial Parkinson's disease were recruited between 1990 and 2021. Patients were genotyped for the presence of mutations in the *SNCA*, *PRKN*, *LRRK2*, or *GBA* genes. Vital status was collected from the National death register for participants born in France. Hazard ratios (HRs) and 95% confidence intervals (CIs) were computed using multivariable Cox proportional hazards regression.

Results: Of the 2,037 patients with Parkinson's disease, 889 had died after a follow-up of up to 30 years. Patients with *PRKN* ($n = 100$, HR = 0.41; $p = 0.001$) and *LRRK2* mutations ($n = 51$, HR = 0.49; $p = 0.023$) had longer survival than those without any mutation, whereas patients with *SNCA* ($n = 20$, HR = 9.88; $p < 0.001$) or *GBA* mutations ($n = 173$, HR = 1.33; $p = 0.048$) had shorter survival.

Interpretation: Survival differs across genetic forms of Parkinson's disease, with higher mortality for patients with *SNCA* or *GBA* mutations, and lower mortality for those with *PRKN* or *LRRK2* mutations. Differences in severity and disease progression among monogenic forms of Parkinson's disease likely explain these findings, which has important consequences for genetic counselling and choice of end points for future clinical trials for targeted therapies.

ANN NEUROL 2023;94:123–132

Introduction

Parkinson's disease (PD) is a multifactorial neurodegenerative disorder characterized by motor and non-motor symptoms. The mortality rate of patients with idiopathic PD is higher than that of the general population and is heterogeneous

between patients.¹ Demographic factors, such as increasing age and male gender, have been associated with higher mortality. Differences in mortality may also be related to disease progression profiles, with some patients having a relatively stable clinical course and others a more rapid progression of

View this article online at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1002/ana.26636). DOI: 10.1002/ana.26636

Received Sep 13, 2022, and in revised form Feb 4, 2023. Accepted for publication Mar 7, 2023.

Address correspondence to Dr Lanore, Sorbonne Université, Institut du Cerveau, Paris Brain Institute, ICM, Inserm, CNRS, 47-83 boulevard de l'Hopital, 75013, Paris, France. E-mail: aymeric.lanore@aphp.fr

[†]Members are listed in the Supplementary Material.

From the ¹Sorbonne Université, Institut du Cerveau—Paris Brain Institute—ICM, Inserm, CNRS, Paris, France; ²Assistance Publique Hôpitaux de Paris, Department of Neurology, CIC Neurosciences, Hôpital Pitié-Salpêtrière, Paris, France; ³Assistance Publique Hôpitaux de Paris, Department of Genetics, Hôpital Pitié-Salpêtrière, Paris, France; ⁴School of Postgraduate Studies, Royal College of Surgeons in Ireland, Dublin, Ireland; ⁵Department of Neurology, Movement Disorder Division, Rush University Medical Center, Chicago, IL; and ⁶Université Paris-Saclay, UVSQ, Univ. Paris-Sud, Inserm, Équipe "Exposome, heredity, Cancer, and Health", CESP, Villejuif, France

Additional supporting information can be found in the online version of this article.

the disease. Indeed, the onset of postural instability and cognitive impairment are considered important milestones in the progression of idiopathic PD, and the dominant tremor phenotype may have a slower progression.² Consistently, higher mortality was reported in patients with idiopathic PD featuring greater motor impairment, cognitive decline, axial signs, and nondominant tremor forms.¹ Autopsies of brains of patients with idiopathic PD have shown an association between motor progression and more advanced neurodegeneration.³ Akineto-rigid dominant phenotype and cognitive impairment were associated with more extensive Lewy body (LB) pathology and more cortical disease.⁴

Genetics allow for a complementary approach to clinically and pathologically subtype patients with PD.⁵ Although PD is commonly sporadic, about 5% to 10% of patients with PD have monogenic forms⁶; with mutations in *SNCA*, *LRRK2*, and *VPS35* being responsible for dominant forms of PD, whereas those mutations in *PRKN*, *PINK1*, and *PARK7* being responsible for recessive forms. *GBA* mutations are considered a strong risk factor for PD.⁷ Although rare and more difficult to study, monogenic forms of PD represent a more homogeneous population in terms of clinical presentation and neuropathological involvement. Only a few studies have examined the specificities of mortality rates in monogenic forms of PD. Compared to idiopathic PD, a single study suggested a better survival in patients with *LRRK2* mutations, whereas data on *GBA* mutations were inconsistent in 2 independent studies.^{8–10} No data on the survival of PD patients with *SNCA* or *PRKN* mutations are available in the literature. By crossing the data from the French registry of death and the French PD genetic network database, our aim was to estimate and compare the mortality rate in patients with PD

with the most frequent *SNCA*, *PRKN*, *LRRK2*, and *GBA* mutations, as compared to patients with PD without pathogenic variants and to the general population.

Materials and Methods

Patients

We used data from the French Parkinson Disease Genetics Network. Patients with PD (fulfilling the UK Brain Bank criteria¹¹) were recruited between 1990 and 2021. As the main objective of this cohort was to identify genetic mutations, it was enriched with patients with familial and early onset PD. Patients were screened for known PD-associated genes using standard genotyping or sequencing methods. Age at onset of PD, gender, and ethnicity were collected. Informed consent was obtained from all participants and the genetic studies were approved by local ethics committees. Vital status until September 6, 2021, was obtained from the French national mortality database, which records deaths of French citizens since 1970.¹²

Genetic Analyses

Patients enrolled between 1990 and 2021 were analyzed by various gene screening techniques, as previously described^{13,14}: between 1990 and 2011, patients with PD were screened by denaturing high-performance liquid chromatography (dHPLC) for *PRKN* and/or by direct Sanger sequencing for *PRKN* (n = 666), *PINK1* (n = 578), *PARK7* (n = 157), whole *LRRK2* (n = 160), *SNCA* (n = 270), and *VPS35* (n = 200 for the whole gene and n = 873 for *VPS35* exon 15) screening. Exon re-arrangements were detected by semiquantitative polymerase chain reaction (PCR) for *PRKN* and *SNCA* or the salsa multiplex ligation-dependent probe amplification method. From 2012, all patients found not to carry any mutations screened by Sanger/MLPA methods and newly recruited patients were analyzed either by targeted sequencing of implemented customized gene

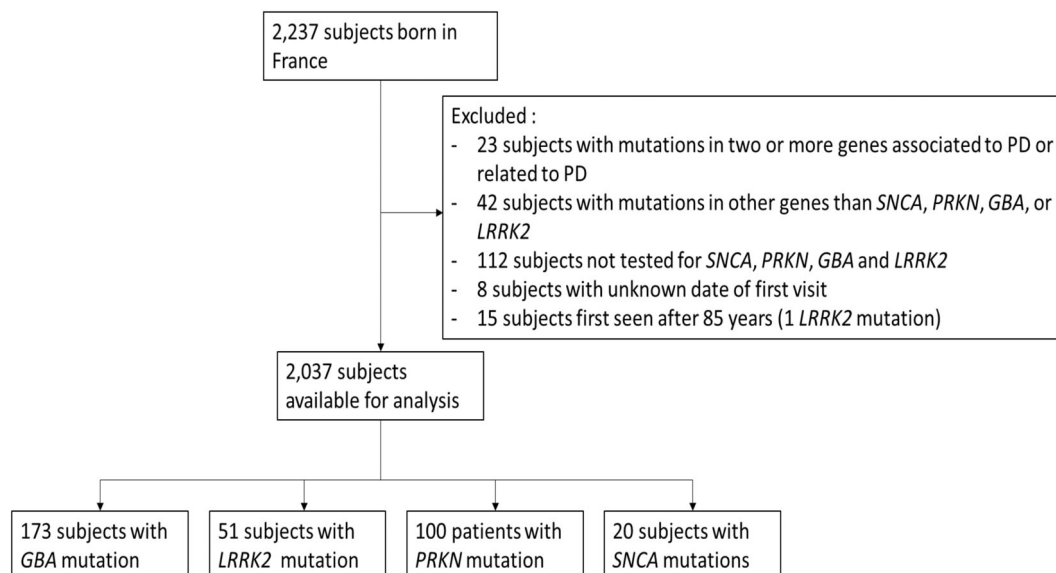


FIGURE 1: Flow chart. PD = Parkinson's disease.

TABLE 1. Characteristics of the Study Population

Mutation	%	Age at onset			Age at first visit			Delay between first visit and onset			Deaths	Age at death		
		F	N	Mean	SD	N	Mean	SD	N	Mean		SD	N	Mean
Total	41.1	1890	50.0	13.2	2037	59.0	13.0	1890	8.8	7.0	889	72.9	9.4	
No mutation ^a	39.9	468	50.3	11.4	476	59.0	11.7	468	8.7	7.0	204	73.4	8.7	
<i>GBA</i>	No	39.6	1,490	48.8	13.4	1,579	58.3	13.2	1,490	9.3	7.3	701	72.8	9.5
	Yes	52.6	169	50.3	11.7	173	58.5	12.1	169	8.1	6.0	92	73.2	8.8
	Mild	53.3	103	51.1	11.1	107	60.3	11.7	103	9.1	6.1	63	73.1	9.3
	Severe	47.2	36	49.6	13.6	36	56.3	12.1	36	6.7	5.6	18	72.3	8.2
	Undetermined	56.7	30	48.5	11.4	30	55.1	12.9	30	6.6	5.5	11	75.1	6.3
	Unknown status ^b	42.8	231	57.1	11.2	285	63.2	11.3	231	6.2	4.5	96	73.8	9.3
<i>LRRK2</i>	No	41.3	1,474	50.4	12.5	1,598	59.6	12.1	1,474	9.0	6.9	739	73.3	8.6
	Yes	41.2	50	51.1	11.9	51	60.1	12.4	50	8.9	6.4	14	74.8	8.9
	Unknown status ^b	40.5	366	48.1	15.9	388	56.4	15.8	366	8.1	7.6	136	70.6	12.6
<i>PRKN</i>	No	42.7	1,408	54.8	11.0	1,422	62.8	11.0	1,408	8.0	6.0	692	74.7	8.0
	Yes	52.0	96	31.5	11.6	100	46.3	13.5	96	14.9	9.9	22	71.0	8.3
	Unknown status ^b	34.8	386	37.1	7.0	515	51.0	12.6	386	10.3	8.4	175	66.3	11.4
<i>SNCA</i>	No	42.5	1,122	46.4	13.0	1,167	55.6	13.0	1,122	9.3	7.5	454	71.6	10.0
	Yes	60.0	19	43.4	8.0	20	49.6	8.3	19	5.7	3.4	14	58.4	10.0
	Unknown status ^b	38.8	749	55.6	11.7	850	63.9	11.2	749	8.2	6.2	421	74.9	7.9

Abbreviation: SD = standard deviation.

^aNo mutation in the *GBA*, *LRRK2*, *PRKN*, and *SNCA* genes.^bNot screened for the corresponding gene.

panels (n = 487, including 77 with panel 4, see supplementary data) and/or whole-exome sequencing (n = 613).

Most patients were screened for the *LRRK2* G2019S mutation using the TaqMan allelic discrimination Assay-By-Design method and/or Sanger sequencing of the *LRRK2* exon 41 (n = 1748). Due to the high homology of *GBA* and its neighboring pseudogene *GBAP*, the whole *GBA* gene was screened by long-range PCR, either by Sanger sequencing (n = 1,407) as previously described¹⁵ or by the next-generation sequencing (NGS) method (n = 316).¹⁶

For genes associated with recessive forms of PD, patients were considered as mutated if mutations are in homozygous, compound heterozygous state (validated by co-segregation analyses), or double heterozygous of unknown phase. *GBA* mutations have been classified as mild or severe: mild mutations are those that cause type I Gaucher Disease, and severe mutations are those that cause type II and III Gaucher Disease.¹⁷ Newly identified variants in this study predicted as "pathogenic" using different in silico algorithms, including the Combined Annotation Dependent

Depletion score (CADD) and benign variants or those of unknown significance were considered as "undetermined."

Statistical Analyses

Analyses were restricted to patients born in France as vital status was only available for French patients,¹² and to patients carrying mutations in *SNCA*, *PRKN*, *GBA*, or *LRRK2*, or without mutations in these genes. We excluded patients (1) with mutations in 2 or more genes associated to PD or related to PD, (2) with mutations in genes other than *SNCA*, *PRKN*, *GBA*, or *LRRK2* (Table S2), (3) not tested for any of the 4 *SNCA*, *PRKN*, *GBA*, and *LRRK2* genes, or (4) for whom baseline visit date was missing. Survival analyses were censored at age 85 years due to potential under-ascertainment of deaths afterward; therefore, we also excluded patients first seen after 85 years of age.

Patients were followed from the baseline visit (entry date into the cohort) until date of death, age of 85 years, or September 6, 2021, whichever occurred first. We used Cox proportional hazards models to compute hazard ratios (HRs) and 95% confidence

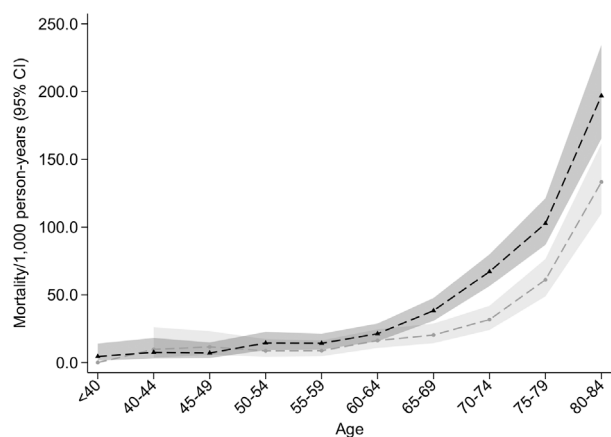


FIGURE 2: Age-specific mortality rates in men and women with Parkinson's disease. Dotted lines represent mortality rates (per 1,000 person-years) and shaded areas their 95% confidence intervals (CIs). Men are depicted with black triangles and women with grey circles.

intervals (CI); we included a random effect (shared frailty) to account for intra-familial correlations. Because patients were not followed since the onset of the disease, the time scale was the time since the first visit, and models were adjusted for age at the first visit (restricted cubic splines), gender, and delay between PD onset

and first visit (coded in quartiles, with a missing category for patients with unknown date of PD onset). Survival proportions were predicted, based on the Cox model.

The model included 4 variables corresponding to the 4 genes, each coded in 3 categories (0 = no mutation; 1 = mutation carrier; and 9 = unknown status for patients who were not tested for the gene). All patients were not tested for the 4 genes; hence, some participants had unknown status for some mutations but not for others. As the 4 genes were included in the same model with a separate category for missing values, patients without mutations in any of the 4 genes represent the reference group for each of the 4 genes; this approach allowed us to exclude from the reference category, patients with a mutation in any of the 4 genes and those not tested for at least one gene. For each gene, we estimated the HR of death in patients with a mutation compared to those without mutations in any of the genes; for these analyses, we did not correct for multiple testing as they are not exploratory and are restricted to the 4 main PD genes that were defined a priori. We then compared the mutations one to another one while correcting for multiple testing (Bonferroni correction). In sensitivity analyses, we examined *GBA* mutations according to their severity. These analyses were performed in patients of all origins and then restricted to those of European origin.

We computed the statistical power of the survival analyses based on the risk of death (43.6% = 889/2037) and the frequency

TABLE 2. Comparison of Mortality Rates in Patients with Parkinson's Disease According to the Type of Mutations and in Patients Without Any Mutation

Mutation	Patients born in France		Patients born in France and of European origin	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
No mutation ^a	1.00 (reference)	–	1.00 (reference)	–
<i>GBA</i>				
Any mutation	1.33 (1.00–1.78)	0.048	1.34 (0.99–1.83)	0.064
Mild	1.27 (0.91–1.79)	0.162	1.27 (0.89–1.81)	0.187
Severe	1.63 (0.89–3.00)	0.114	1.76 (0.90–3.42)	0.097
Undetermined	1.24 (0.57–2.67)	0.584	1.27 (0.57–2.83)	0.563
Mild + Undetermined	1.27 (0.92–1.75)	0.144	1.27 (0.91–1.77)	0.161
Severe ^b	1.63 (0.89–3.00)	0.114	1.76 (0.90–3.42)	0.097
	<i>p</i> -trend	0.114	<i>p</i> -trend	0.097
<i>LRRK2</i>	0.49 (0.26–0.90)	0.023	0.32 (0.14–0.73)	0.006
<i>PRKN</i>	0.41 (0.24–0.70)	0.001	0.38 (0.22–0.66)	0.001
<i>SNCA</i>	9.88 (4.78–20.40)	< 0.001	9.49 (4.27–21.10)	< 0.001

Note. HRs and 95% CIs computed using a multivariable Cox proportional hazards model with shared frailty that includes all the mutations in the same model. We used time since first visit as the time scale, and models were adjusted for age (restricted cubic splines), sex, delay between onset and first visit (in quartiles), and a random effect (frailty variance $\theta = 0.494$, standard error = 0.117, $p < 0.001$). Patients without mutations in *GBA*, *LRRK2*, *PRKN*, and *SNCA* represent the reference group.

^aNo mutation in the *GBA*, *LRRK2*, *PRKN*, and *SNCA* genes.

^bSevere versus mild + undetermined: $p = 0.454$; in Europeans only: $p = 0.371$.

Abbreviation: CI = confidence interval; HR = hazard ratio.

of mutations in the four genes for a range of HRs (Fig S1). Statistical power varied across different genes and was lowest to detect $HR < 2$ for *SNCA*, followed by *GBA* undetermined and *GBA* severe categories.

Finally, we computed standardized mortality ratios (SMRs; standardized by sex, 5 year age group, and calendar year) to compare mortality rates in patients with PD, overall and by mutation, to those from the French general population.¹⁸ The SMR is the ratio of the number of deaths observed in a population over a given period to the number that would be expected over the same period if the study population had the same age- and sex-specific rates as the standard population. If the SMR is > 1 , it is interpreted as excess mortality in the study population, whereas an $SMR < 1$ corresponds to lower than expected mortality.

Results

Of the 2,237 patients born in France, we excluded 23 patients with mutations in 2 or more genes associated to PD or related to PD, 42 patients with mutations

in genes other than *SNCA*, *PRKN*, *GBA*, or *LRRK2* (Table S2), 112 patients were not tested for any of the 4 genes, 8 patients with an unknown date of first visit, and 15 patients first seen after 85 years (Fig 1). We included in the analyses 2,037 patients (41.1% women; 91.9% of European origin) from 1,304 families: 771 families included one patient, 372 with 2 patients; 133 with 3 patients; and 28 included ≥ 4 patients. Of these patients, 20 had *SNCA* mutations, 100 had *PRKN* mutations (38 with homozygous mutations, 41 with compound heterozygous mutations, and 21 with double heterozygous *PRKN* mutations), 173 had *GBA* mutations and 51 had *LRRK2* G2019S mutations (see Fig 1). Patient characteristics and their genetic status are shown in Table 1. At baseline, patients with *SNCA* (49.6 years, standard deviation [SD] = 8.3) or *PRKN* mutations (46.3 years, SD = 13.5) were younger than patients with *GBA* (58.5 years, SD = 12.1) or *LRRK2* mutations (60.1 years, SD = 12.4) or those without any mutation

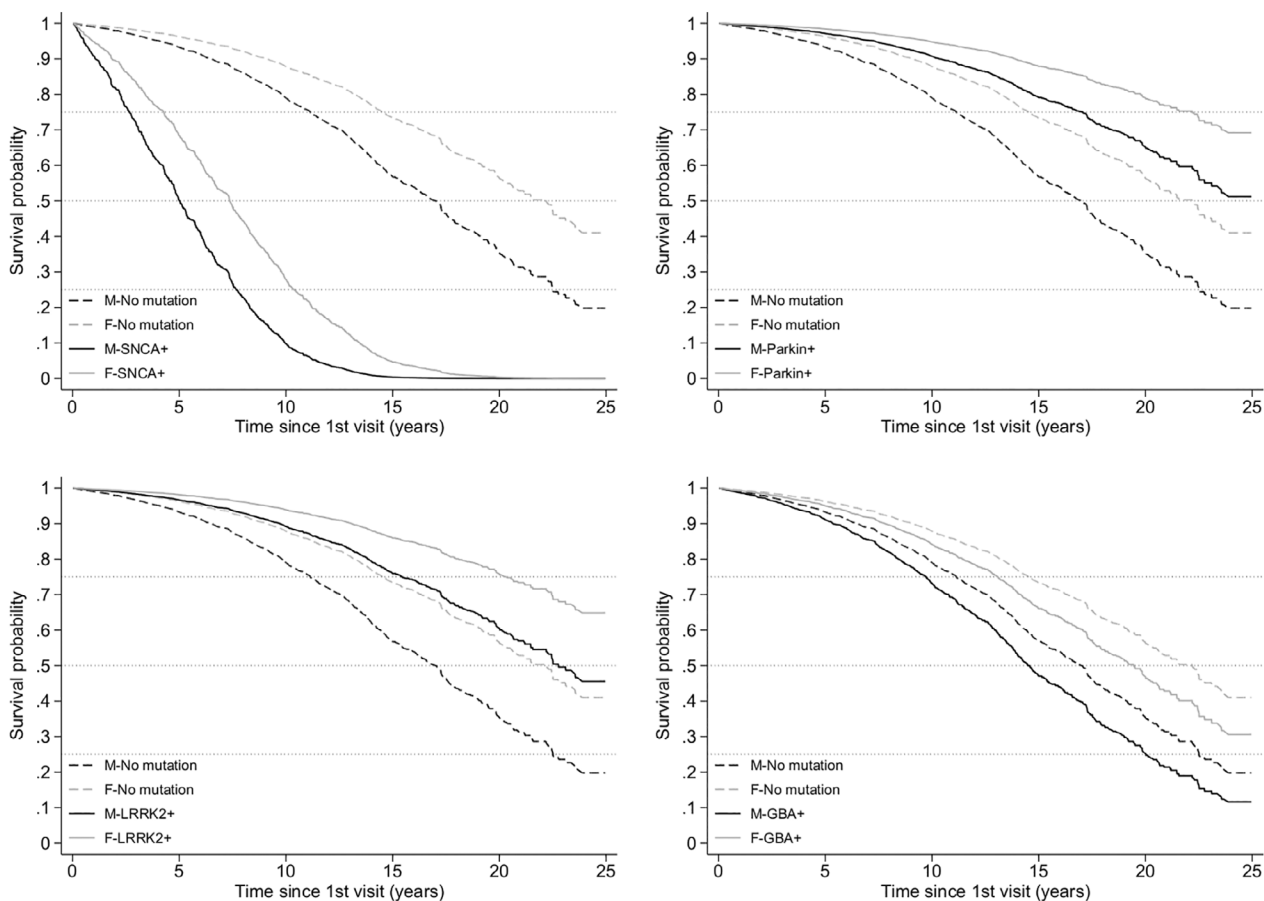


FIGURE 3: Predicted survival probabilities in patients with Parkinson's disease by type of mutations compared to parkinsonian patients without any mutation. M, males; F, females. No mutation: No mutation in the *GBA*, *LRRK2*, *PRKN*, and *SNCA* genes. Survival probabilities (%) since the first visit until the end of the study are predicted by the Cox model with shared frailty for men and women aged 60 years old at the first visit and in the first quartile of the delay between the first visit and PD onset (0 to 3.6 years, mean = 2.0, standard deviation = 0.9). The horizontal lines represent the percentiles of the survival times (25th, 50th [median survival], and 75th). Survival analyses were censored at the age of 85 years.

TABLE 3. Percentiles of Survival Curves in Men and Women by Age at First Visit and by Type of Mutations

Age at first visit	Mutation	Percentiles of survival curves					
		Men			Women		
		75th	50th	25th	75th	50th	25th
40	No mutation*	20.7	-	-	-	-	-
	<i>GBA</i>	18.3	-	-	23.6	-	-
	<i>LRRK2</i>	-	-	-	-	-	-
	<i>PRKN</i>	-	-	-	-	-	-
	<i>SNCA</i>	6.8	11.0	15.0	9.5	15.0	19.9
45	No mutation*	19.2	-	-	25.7	-	-
	<i>GBA</i>	17.1	25.7	-	22.2	-	-
	<i>LRRK2</i>	-	-	-	-	-	-
	<i>PRKN</i>	-	-	-	-	-	-
	<i>SNCA</i>	6.1	9.9	13.8	8.6	13.4	18.1
50	No mutation*	17.1	25.7	-	22.2	-	-
	<i>GBA</i>	14.6	22.3	-	19.5	-	-
	<i>LRRK2</i>	22.8	-	-	-	-	-
	<i>PRKN</i>	25.7	-	-	-	-	-
	<i>SNCA</i>	5.0	8.6	12.2	7.4	11.6	16.1
55	No mutation*	13.9	20.6	-	18.3	-	-
	<i>GBA</i>	12.4	18.3	25.7	16.1	23.6	-
	<i>LRRK2</i>	19.5	-	-	-	-	-
	<i>PRKN</i>	20.6	-	-	-	-	-
	<i>SNCA</i>	3.8	6.8	9.9	5.8	9.4	13.4
60	No mutation*	11.1	16.8	22.5	14.4	21.6	-
	<i>GBA</i>	9.6	14.5	20.0	13.0	19.2	-
	<i>LRRK2</i>	15.3	22.5	-	20.1	-	-
	<i>PRKN</i>	16.8	-	-	21.6	-	-
	<i>SNCA</i>	2.6	5.0	7.6	4.2	7.4	10.3
65	No mutation*	8.4	13.2	17.9	11.4	17.3	23.1
	<i>GBA</i>	7.4	11.4	15.8	9.9	14.9	20.0
	<i>LRRK2</i>	12.2	18.1	-	16.1	-	-
	<i>PRKN</i>	13.2	19.8	-	17.3	-	-
	<i>SNCA</i>	1.7	3.4	5.7	2.8	5.2	8.0

Note: Percentiles of survival curves were determined based on survival probabilities since first visit (age comprised between 40 to 65 years) until the end of the study (maximum follow-up of 30 years) predicted by the Cox model with shared frailty for men and women in the first quartile of delay between age at first visit and PD onset (0 to 3.6 years, mean = 2.0, standard deviation = 0.9). Patients were followed until a maximum age of 85 years.

Empty cells correspond to situations in which the percentage of patients alive at the end of the follow-up was greater than the corresponding percentile.

TABLE 4. SMRs Overall and According to the Type of Mutations

Mutation	O	E	SMR (95% CI)	<i>p</i>	PD cases with delay between onset and first visit ≤ 5 years			
					O	E	SMR (95% CI)	<i>p</i>
All cases	889	342.0	2.6 (2.4–2.8)	< 0.0001	220	102.3	2.1 (1.9–2.4)	< 0.0001
No mutation ^a	204	84.3	2.4 (2.1–2.8)	< 0.0001	56	28.0	2.0 (1.5–2.5)	0.0002
<i>GBA</i>	92	26.7	3.4 (2.7–4.2)	< 0.0001	25	8.5	2.9 (1.8–4.1)	0.0010
<i>LRRK2</i>	14	11.1	1.3 (0.6–1.9)	0.4411	2	3.1	0.6 (0.1–1.5)	0.4449
<i>PRKN</i>	22	13.4	1.6 (0.9–2.3)	0.0670	2	1.1	1.8 (0.1–4.2)	0.5441
<i>SNCA</i>	14	0.8	16.5 (7.9–25.1)	0.0004	6	0.2	28.1 (5.6–50.4)	0.0182

Note: SMRs were computed by using mortality rates from the French population, by sex, 5-year age groups, and calendar time.

^aNo mutation in the *GBA*, *LRRK2*, *PRKN*, and *SNCA* genes.

Abbreviation: CI = confidence interval; E = expected number of deaths; O = observed number of deaths; PD = Parkinson's disease; SMRs = standardized mortality ratios.

(59.0 years, SD = 13.2). After a mean follow-up of 11.8 years (SD = 6.2, range = 1–30), 889 patients died (mortality rate = 37.1/1000 person-years, 95% CI = 34.7–39.6). Mortality rates were higher in men than in women and increased with age (Fig 2).

Patients with *LRRK2* (HR = 0.49; *p* = 0.023) or *PRKN* (HR = 0.41; *p* = 0.001) mutations had longer survival than those without any mutation, whereas patients with *SNCA* (HR = 9.9; *p* < 0.001) or *GBA* (HR = 1.3; *p* = 0.048) mutations had shorter survivals (Table 2, Fig 3). Similar findings were obtained in analyses restricted to European patients (see Table 2). For types of *GBA* mutations, HRs were higher for severe than mild or undetermined mutations, but none of the HRs were statistically significant (see Table 2).

Survival was similar for patients with *LRRK2* and *PRKN* mutations (HR = 1.18, 95% CI = 0.53–2.58, *p* = 0.6891). Alternatively, patients with *SNCA* mutations had worse survival than those with any of the other mutations (*GBA*, HR = 7.43, 95% CI = 3.50–15.77, *p* = 1.7×10^{-7} ; *LRRK2*, HR = 20.36, 95% CI = 7.98–51.92, *p* = 2.8×10^{-10} ; and *PRKN*, HR = 23.92, 95% CI = 10.11–56.60, *p* = 4.8×10^{-13}). Patients with *GBA* mutations had a worse survival than those with *LRRK2* (HR = 2.74, 95% CI = 1.41–5.29, *p* = 0.0027) and *PRKN* mutations (HR = 3.22, 95% CI = 1.94–5.63, *p* = 4.1×10^{-5}). These differences remained significant after correction for multiple testing (*p*-Bonferroni = 0.05/6 = 0.0083).

Table 3 shows estimates of the median survival. For instance, in men aged 65 years at the first visit, the median survival for patients without any mutations was 13.2 years, whereas it increased to 19.8 years for patients with *PRKN* mutations and to 18.1 years for patients with *LRRK2*

mutations; the median survival for patients with *GBA* mutations was reduced to 11.4 years, and it was only 3.4 years for patients with *SNCA* mutations (see Table 3).

We then compared survival of patients with PD of our cohort, with and without mutations, to the French general population. The SMR was 2.6 (95% CI = 2.4–2.8) overall and 2.4 (95% CI = 2.1–2.8) in patients without any mutation (Table 4). The highest SMRs were seen for *SNCA* (16.5, 95% CI = 7.9–25.1) followed by *GBA* (3.4, 95% CI = 2.7–4.2). SMRs were greater than 1 but considerably smaller and not statistically significant for *PRKN* (1.6, 95% CI = 0.9–2.3) and *LRRK2* (1.3, 95% CI = 0.6–1.9). Overall, the SMR decreased slightly in analyses restricted to patients with a delay between the onset and the first visit ≤ 5 years (2.1, 95% CI = 1.9–2.4), likely due to the inclusion of patients with less advanced PD.

Discussion

Compared with patients without any mutation, patients with *PRKN* or *LRRK2* mutations had increased survival whereas patients with *SNCA* or *GBA* mutations showed reduced survival. SMRs were consistent with these results, with *SNCA* and *GBA* mutations showing a strong effect on mortality compared to the general population, whereas *PRKN* and *LRRK2* mutations had a considerably weaker effect. To our knowledge, this is the first study to compare mortality across mutated genes associated with PD, and to provide survival estimates for patients with *SNCA* and *PRKN* mutations.

Longer survival in patients with *PRKN* compared with patients without any mutations is consistent with the relatively benign, predominantly motor, course of the disease.^{13,19} Although earlier in onset, the progression of motor impairment

in patients with bi-allelic *PRKN* mutations is slower, with cognitive impairment and autonomic nervous system dysfunction less pronounced than in patients with idiopathic PD.^{20–22} This pattern of progression may be related to neuronal loss limited primarily to the substantia nigra and the absence of alpha synuclein neuronal inclusions on pathology.²³

By contrast, in our study, patients with *SNCA* mutations had shorter survival compared to those without any mutations and higher mortality compared to the general population. A previous study of 32 patients with the *SNCA* G209A mutation reported a mean survival of 9.7 years (SD = 3.8) after disease onset, which is consistent with the survival distribution we found for patients with *SNCA* mutations.²⁴ The latter appear to have more severe motor and non-motor progression with severe cardiovascular autonomic dysfunction²⁰ and early cognitive decline.^{25,26} Moreover, patients with *SNCA* mutations have diffuse alpha synuclein aggregates and cortical involvement that can lead to rapid disease progression and differential mortality.²³

The better survival of patients with the *LRRK2* G2019S mutation we observed is consistent with a previous report of 159 patients with *LRRK2* mutations showing a trend toward longer survival compared with 1,088 patients with idiopathic PD.¹⁰ These findings are consistent with *LRRK2* mutations being associated with slower motor decline and milder cognitive impairment compared to those with idiopathic PD.^{21,27} At the pathological level, LBs may be absent from some patients carrying *LRRK2* mutations.²³

Mortality data are more controversial for *GBA* mutations. Similar to our findings, a study of 123 patients with *GBA* mutations reported an HR of 1.85 (95% CI = 1.2–2.8) and a trend toward higher mortality for severe mutations.⁹ Two smaller studies also found increased mortality.^{8,28} On the other hand, one study comparing the survival of 148 mild and 43 severe *GBA*-mutated patients with 1,088 patients with idiopathic PD found no effect of these mutations on mortality.¹⁰ Our findings are in favor of a higher mortality for patients carrying *GBA* mutations. The observed trend toward higher mortality for severe *GBA* mutations supports our main findings. *GBA* mutations have also been associated with worse PD progression and non-motor symptoms, such as cardiovascular autonomic dysfunction²⁰ and cognitive decline,²⁹ supporting the hypothesis that higher mortality is likely due to more severe progression. Pathologically, *GBA* mutations were associated with widespread cortical LBs.²³

Although patients with *PRKN* and *SNCA* mutations had earlier PD onset, we showed that their survival differed widely, suggesting that age of onset is not the main prognostic factor in these monogenic forms. *SNCA* and *GBA* mutations are more strongly associated with LB

pathology and a more rapid motor and non-motor progression than *PRKN* and *LRRK2* mutations.

In patients with idiopathic PD, cognitive decline has been associated with increased mortality.¹ Pneumonia has been consistently identified as a major cause of death of patients with PD, accounting for 20% to 30% of deaths.^{30–34} In PD, the presence of cognitive impairment is associated with a higher incidence of aspiration pneumonia, which may explain the higher mortality.³⁵ Autonomic dysfunction has been associated with shorter survival in idiopathic PD, possibly mediated by falls and the resulting consequences.³⁶ Beyond their association with PD progression, mutations in *SNCA* or *GBA* genes could lead to death by non-neurological mechanisms, such as sudden cardiac arrest. However, sudden cardiac arrest seems to be rare in patients with PD.³¹ These hypotheses need to be confirmed by cause-of-death analyses, which were not available in our study.

Our results have several important clinical implications. First, in genetic counselling, although genetic results do not yet lead to a change in treatment, it allows patients to have a more accurate prediction of the progression of their disease³⁷ and enhances practitioners' awareness of the management of mutation specific complications, including autonomic disorders and cognitive impairment. Second, our results could have an important impact in drug development designs for upcoming precision clinical trials,³⁸ in particular on the use of survival as an end point for rapidly progressive forms of PD linked to *SNCA* mutations.

However, our study has some limitations. First, analyses were performed using time since the first visit rather than from the onset of PD. For most patients, the baseline visit occurred several years after disease onset, which may lead to include patients who survived until study entry (survival bias). Therefore, to address this issue, analyses were adjusted for age at onset and time from symptom onset to inclusion. Second, because vital status was only available for patients born in France, the population is mostly European, which may have led to under-representation of certain genetic mutations, such as *LRRK2*.³⁹ Third, our cohort enriched with familial and early age at onset of patients with PD may not be representative of the general PD population. However, the SMR of the whole cohort was very similar to what has been described in an early onset PD population.⁴⁰ Fourth, the small number of patients with *SNCA* mutations led to imprecise point estimates due to wide CIs. Statistical power varied across different genes, and was lowest to detect small effects for *SNCA*, followed by *GBA* with undetermined and severe types, which hampered our ability to examine the influence of *GBA* mutations'

severity. Fifth, our analyses were not adjusted for important risk factors of death, in particular cardiovascular risk factors. As the frequency of these risk factors may be different in different ethnic groups, we restricted the analyses to patients of European origin and found similar results. Sixth, heterogeneity in the gene screening methods used led to some patients not being tested for all 4 genes and may have led to an under identification of mutations in other genes. However, whether patients were screened or not for a gene is non-differential with respect to vital status, and this would bias associations toward the null. In addition, other genetic factors may be involved in survival, such as single nucleotide polymorphisms (SNPs) in apolipoprotein E associated to survival in the general population⁴¹ and the polygenic risk score for PD associated with faster cognitive decline and progression of motor symptoms.⁴² Further studies taking genetic and non-genetic factors into account could be carried out.

In conclusion, survival differs across genetic forms of PD, with poorer survival for mutations linked to more aggressive forms (*SNCA* and *GBA*), and longer survival for those associated with a more benign disease course (*PRKN* and *LRRK2*). Our results suggest that mortality is related to disease progression rather than age at onset, which is of major importance for prognosis and genetic counselling. With the emergence of therapies targeting monogenic PD, these results also provide a basis for the design of future precision clinical trials.

Acknowledgments

This work was supported by the Fondation pour la Recherche Médicale (FRM, MND202004011718), the Fondation de France, France-Parkinson Association, la Fédération pour la Recherche sur le Cerveau (FRC) and the French program “Investissements d’avenir” (ANR-10-IAIHU-06).

Author Contributions

A.L., F.C., S.L., A.B., A.E., and J.C. contributed to the conception and design of the study. A.L., F.C., C.T., T.C., S.S., G.M., L.M., S.L., A.B., A.E., and J.C. contributed to the acquisition and analysis of data. A.L., F.C., C.T., P.M., S.L., A.B., A.E., and J.C. contributed to drafting the text or preparing the figures. All authors have read and agreed to the published version of the manuscript.

Study Group: The French clinicians’ network for PD genetics (the PDG group) members (Supplementary file).

References

- Macleod AD, Taylor KSM, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 2014;29:1615–1622.
- Evans JR, Mason SL, Williams-Gray CH, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. *J Neurol Neurosurg Psychiatry* 2011;82:1112–1118.
- Braak H, Rüb U, Jansen Steur ENH, et al. Cognitive status correlates with neuropathologic stage in Parkinson disease. *Neurology* 2005; 64:1404–1410.
- Selikhova M, Williams DR, Kempster PA, et al. A clinico-pathological study of subtypes in Parkinson's disease. *Brain* 2009;132:2947–2957.
- Greenland JC, Williams-Gray CH, Barker RA. The clinical heterogeneity of Parkinson's disease and its therapeutic implications. *Eur J Neurosci* 2019;49:328–338.
- Reed X, Bandrés-Ciga S, Blauwendraat C, Cookson MR. The role of monogenic genes in idiopathic Parkinson's disease. *Neurobiol Dis* 2019;124:230–239.
- Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med* 2009;361:1651–1661.
- Brockmann K, Srujijes K, Pfliederer S, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. *Mov Disord* 2015;30:407–411.
- Cilia R, Tunesi S, Marotta G, et al. Survival and dementia in GBA-associated Parkinson's disease: the mutation matters. *Ann Neurol* 2016;80:662–673.
- Thaler A, Kozlovski T, Gurevich T, et al. Survival rates among Parkinson's disease patients who carry mutations in the LRRK2 and GBA genes: PD survival with gene mutations. *Mov Disord* 2018;33:1656–1660.
- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*. juin 1988;51(6):745–52.
- Fichier des personnes décédées (Décès). data.gouv.fr [Internet]. [cité 21 juill 2022]. Disponible sur: <https://www.data.gouv.fr/en/datasets/fichier-des-personnes-decedees/>.
- Lesage S, Lunati A, Houot M, et al. Characterization of recessive Parkinson disease in a large multicenter study. *Ann Neurol* 2020;88:843–850.
- Lesage S, Houot M, Mangone G, et al. Genetic and phenotypic basis of autosomal dominant Parkinson's disease in a large multi-center cohort. *Front Neurol* 2020;11:682.
- Lesage S, Anheim M, Condroyer C, et al. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. *Hum Mol Genet* 2011;20:202–210.
- Zampieri S, Cattarossi S, Bembi B, Dardis A. GBA analysis in next-generation era: pitfalls, challenges, and possible solutions. *J Mol Diagn* 2017;19:733–741.
- Beutler E, Gelbart T, Scott CR. Hematologically important mutations: Gaucher disease. *Blood Cells Mol Dis* 2005;35:355–364.
- Taux de mortalité par sexe et âge [Internet]. Ined - Institut national d'études démographiques. [cité 4 avr 2022]. Disponible sur: <https://www.ined.fr/fr/tout-savoir-population/chiffres/france/mortalite-cause-deces/taux-mortalite-sexe-age/>.
- Lohmann E, Periquet M, Bonifati V, et al. How much phenotypic variation can be attributed to parkin genotype? *Ann Neurol* 2003;54:176–185.
- Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: implications for pathophysiology, diagnosis, and treatment. *Neurobiol Dis* 2020;134:104700.
- Planas-Ballvé A, Vilas D. Cognitive impairment in genetic Parkinson's disease. *Parkinsons Dis* 2021;2021:8610285.
- Sun YM, Yu HL, Zhou XY, et al. Disease progression in patients with Parkin-related Parkinson's disease in a longitudinal cohort. *Mov Disord* 2021;36:442–448.

23. Schneider SA, Alcalay RN. Neuropathology of genetic synucleinopathies with parkinsonism: review of the literature. *Mov Disord* 2017;32:1504–1523.
24. Papapetropoulos S, Paschalis C, Ellul J, et al. Survival duration of Parkinson's disease patients living in Greece who carry the G209A α -synuclein mutation. *Mov Disord* 2002;17:847–848.
25. Fuchs J, Nilsson C, Kachergus J, et al. Phenotypic variation in a large Swedish pedigree due to SNCA duplication and triplication. *Neurology* 2007;68:916–922.
26. Book A, Guella I, Candido T, et al. A meta-analysis of α -synuclein multiplication in Familial Parkinsonism. *Front Neurol* 2018;9:1021.
27. Saunders-Pullman R, Mirelman A, Alcalay RN, et al. Progression in the LRRK2-associated Parkinson disease population. *JAMA Neurol* 2018;75:312–319.
28. Stoker TB, Camacho M, Winder-Rhodes S, et al. Impact of GBA1 variants on long-term clinical progression and mortality in incident Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2020;91:695–702.
29. Liu G, Boot B, Locascio JJ, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. *Ann Neurol* 2016;80:674–685.
30. Hely MA, Reid WGJ, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. *Mov Disord* 2008;23:837–844.
31. Beyer MK, Herlofson K, Arsland D, Larsen JP. Causes of death in a community-based study of Parkinson's disease. *Acta Neurol Scand* 2001;103:7–11.
32. Fall PA, Saleh A, Fredrickson M, et al. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. *Mov Disord* 2003;18:1312–1316.
33. D'Amelio M, Ragonese P, Morgante L, et al. Long-term survival of Parkinson's disease: a population-based study. *J Neurol* 2006;253:33–37.
34. Pinter B, Diem-Zangerl A, Wenning GK, et al. Mortality in Parkinson's disease: a 38-year follow-up study. *Mov Disord* 2015;30:266–269.
35. Won JH, Byun SJ, Oh BM, et al. Risk and mortality of aspiration pneumonia in Parkinson's disease: a nationwide database study. *Sci Rep* 2021;11:6597.
36. De Pablo-Fernandez E, Tur C, Revesz T, et al. Association of Autonomic Dysfunction with Disease Progression and Survival in Parkinson disease. *JAMA. Neurology* 2017;74:970–976.
37. Alcalay RN, Kehoe C, Shorr E, et al. Genetic testing for Parkinson disease: current practice, knowledge, and attitudes among US and Canadian movement disorders specialists. *Genet Med* 2020;22:574–580.
38. Schneider SA, Alcalay RN. Precision medicine in Parkinson's disease: emerging treatments for genetic Parkinson's disease. *J Neurol* 2020;267:860–869.
39. Li JQ, Tan L, Yu JT. The role of the LRRK2 gene in parkinsonism. *Mol Neurodegener* 2014;9:47.
40. Hustad E, Myklebust TÅ, Gulati S, Aasly JO. Increased mortality in young-onset Parkinson's disease. *J Mov Disord* 2021;14:214–220.
41. Deelen J, Evans DS, Arking DE, et al. A meta-analysis of genome-wide association studies identifies multiple longevity genes. *Nat Commun* 2019;10:3669.
42. Paul KC, Schulz J, Bronstein JM, et al. Association of Polygenic Risk Score with Cognitive Decline and Motor Progression in Parkinson disease. *JAMA Neurol* 2018;75:360–366.

Appendix A

The French Clinicians' network for Parkinson's Disease Genetics (the PDG Group) Members

Yves Agid (site investigator, Department of Neurology, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Mathieu Anheim (site investigator, Department of Neurology, University Hospital, Strasbourg, France), Michel Borg (site investigator, Department of Neurology, University Hospital, Nice, France), Alexis Brice (site investigator, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Emmanuel Broussolle (site investigator, Department of Neurology, Civil Hospices of Lyon, Lyon, France), Jean-Christophe Corvol (site investigator, Centre for Clinical Investigations, CIC-1422, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Philippe Damier (site investigator, Centre for Clinical Investigations, CIC-0004, Laennec Hospital, Nantes, France), Luc Defebvre (site investigator, Department of Neurology and Pathology of the Movements, Roger Salengro Hospital, Lille, France), Alexandra Dürr (site investigator, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Franck Durif (site investigator, Department of Neurology, University Hospital Center, Clermont-Ferrand, France), Jean Luc Houeto (site investigator, Department of Neurology, Centre for Clinical Investigations, CIC-1402, University Hospital, Poitiers, France), Paul Krack (site investigator, Department of Neurology, University Hospital, Bern, Switzerland), Stephan Klebe (site investigator, Department of Neurology, University Hospital, Essen, Germany), Suzanne Lesage (site investigator, INSERM Unit 1,127, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Ebba Lohmann (site investigator, Department of Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, Tübingen, Germany), Maria Martinez (site investigator, INSERM Unit 563, Toulouse, France), Graziella Mangone (site investigator, Centre for Clinical Investigations, CIC-1422, Pitié-Salpêtrière Hospital, Paris, France), Louise-Laure Mariani (site investigator, Centre for Clinical Investigations, CIC-1422, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France), Pierre Pollak (site investigator, Department of Neurology, University Hospital Center, Grenoble, France), Olivier Rascol (site investigator, Departments of Neurosciences and Clinical Pharmacology, Clinical Investigation Center CIC 1436, University Hospital, Toulouse, France), François Tison (site investigator, Department of Neurology, University Hospital, Bordeaux, France), Christine Tranchant (site investigator, Department of Neurology, University Hospital, Strasbourg, France), Marc Vérin (site investigator, Department of Neurology, University Hospital, Rennes, France), François Viallet (site investigator, Department of Neurology, University Hospital of Aix-Pertuis, Aix-en-Provence, France), and Marie Vidailhet (site investigator, Department of Neurology, Paris Brain Institute, Pitié-Salpêtrière Hospital, Paris, France).