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Low prevalence of known pathogenic mutations in dominant PD genes: A Swedish multicenter study

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A B S T R A C T

Objective: To determine the frequency of mutations known to cause autosomal dominant Parkinson disease (PD) in a series with more than 10% of Sweden's estimated number of PD patients.

Methods: The Swedish Parkinson Disease Genetics Network was formed as a national multicenter consortium of clinical researchers who together have access to DNA from a total of 2,206 PD patients; 85.4% were from population-based studies. Samples were analyzed centrally for known pathogenic mutations in *SNCA* (duplications/triplications, p.Ala30Pro, p.Ala53Thr) and *LRRK2* (p.Asn1437His, p.Arg1441His, p.Tyr1699Cys, p.Gly2019Ser, p.Ile2020Thr). We compared the frequency of these mutations in Swedish patients with published PD series and the gnomAD database.

Results: A family history of PD in first- and/or second-degree relatives was reported by 21.6% of participants. Twelve patients (0.54%) carried *LRRK2* p.(Gly2019Ser) mutations, one patient (0.045%) an *SNCA* duplication. The frequency of *LRRK2* p.(Gly2019Ser) carriers was 0.11% in a matched Swedish control cohort and a similar 0.098% in total gnomAD, but there was a marked difference between ethnicities in gnomAD, with 42-fold higher frequency among Ashkenazi Jews than all others combined.

Conclusions: In relative terms, the *LRRK2* p.(Gly2019Ser) variant is the most frequent mutation among Swedish or international PD patients, and in gnomAD. *SNCA* duplications were the second most common of the mutations examined. In absolute terms, however, these known pathogenic variants in dominant PD genes are generally very rare and can only explain a minute fraction of familial aggregation of PD. Additional genetic and environmental mechanisms may explain the frequent co-occurrence of PD in close relatives.

1. Introduction

Heterozygous sequence alterations in *LRRK2,* as well as sequence or copy number variants (CNV) in *SNCA*, cause monogenic Parkinson's disease (PD) with autosomal dominant inheritance [1,2]. *LRRK2* p.(Gly2019Ser) is considered the most common mutation that markedly increases PD risk in carriers [3–5]. Large variation in the frequency of *LRRK2* p.(Gly2019Ser) in PD patients has been reported from different

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studies and different populations, ranging from 0% to above 40% [6]. In Sweden, only a small number of patients have been identified with this mutation in clinical practice and in research studies [7]. *SNCA* duplications or triplications have been found in more than 50 families world-wide [8]. Other established causes of autosomal dominant PD are exceptionally rare and most have only been reported from a few families world-wide [9,10]. This contrasts markedly with a consistently large proportion of at least 10–15% of PD patients reporting positive family history for PD.

Despite many years of research on the monogenic causes of PD internationally, there are few published reports on systematic screening of larger, population-based sample collections for pathogenic variants in more than one gene. Thus, the overall burden of these mutations in PD patients is hard to estimate, and it is difficult to appreciate the relative frequency of various known causes of autosomal dominant PD. We aimed at establishing the frequency of known pathogenic mutations in both *LRRK2* and *SNCA*, including *SNCA* CNVs, in a large, representative proportion of Swedish PD patients, and compare this with the proportion of patients with familial aggregation of PD. Further, we reviewed previous studies reporting systematic screening of PD case series for variants in more than one dominant PD gene, and retrieved information on the frequency of these mutations from a large genetic database.

2. Methods

All major clinical research centers in Sweden were contacted and those who had access to DNA from PD patients were invited to participate in this collaborative multicenter study. All study participants had been enrolled and provided written informed consent to their participation in the respective contributing centers' research programs, with ethical approval from the regional ethical review boards. Analysis of GBA variants in a subset of 1,625 cases from these collections has previously been reported [11].

Swedish population data was retrieved from the population database at Statistics Sweden (https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/).

Samples were transferred to one site, Lund, and genetic analyses were performed at the Department of Clinical Genetics, Regional and University Laboratories, Lund (E.L.-A., E.M., J.K., M.So.), and/or at the Translational Neurogenetics Unit, Lund University (I.J-F., R.M., M.Sw.).

Seven point mutations in *SNCA* (NM_000345.3) and *LRRK2* (NM_198,578.3) were analyzed with validated TaqMan SNP Genotyping Assays (Life Technologies Europe): *SNCA* c.88G > C p.(Ala30Pro), rs104893878; c.157G > A p.(Ala53Thr), rs104893877; *LRRK2* c.4309A > C p.(Asn1437His), rs74163686; c.4322G > A p.(Arg1441His), rs34995376; c.5096A > G p.(Tyr1699Cys), rs35801418; c.6055G > A p.(Gly2019Ser), rs34637584; and c.6059T > C p.(Ile2020Thr), rs35870237 (Supplementary Table 1). Positive control samples were available for *SNCA* c.157G > A [12], for *LRRK2* c.4309A > C as provided by M.T., and for *LRRK2* c.6055G > A by A.C.B [7]. PCR amplification (Supplementary Table 2) was performed on Veriti Thermal Cycler with post-read performed on a 7500 Fast Real-Time PCR system (Applied Biosystems) or a CFX96 system (CFX96tm Real-Time System, Bio-Rad Laboratories, USA). Data was analyzed using TaqManGenotyper Software. Duplicates of samples were analyzed in each cohort. Twenty-seven samples that were tentatively positive in the TaqMan assays were analyzed by Sanger sequencing (Eurofins Genomics GmbH, Germany).

Analysis of *SNCA* CNV was performed by two different methods. The majority (1,556) of samples were analyzed by digital droplet PCR, using predesigned PrimePCR ddPCR CNV Assays (Bio-Rad Laboratories). An additional 685 samples, plus 24 that were tentatively positive in digital PCR, were tested with TaqMan CNV analysis, using real-time polymerase chain reaction and unquenching of fluorescent probes for *SNCA* (TaqMan Copy Number Assay ID: Hs03506784_cn) and the ribonuclease P RNA component H1 gene *RPPH1* (TaqMan assay no. 4403326) as reference. Each sample was run in quadruplicates on an Applied Biosystems real-time PCR system and analyzed using CopyCaller software. Some samples were analyzed repeatedly and/or with both methods. DNA from known carriers of heterozygous *SNCA* duplication from the Swedish Lister Family [13,14] was used as positive controls, and no template controls were used in all assays. Eight samples showing a tentative *SNCA* copy number anomaly with either ddPCR and/or TaqMan analysis were tested with a Multiple Ligation Probe Amplification assay according to the protocol (MDP version-006) issued by the manufacturer (MLPA, kit P051, MRC Holland, The Netherlands) [15].

Clinical data was extracted from medical records, self-reported by patients during study interviews or in questionnaires, and/or obtained through neurological examination and study visits by a movement disorder specialist, neurologist, and/or study nurse (Table 1). This was partially complemented with data from the Swedish Parkinson Register (http://neuroreg.se/en.html/parkinsons-disease).

LRRK2 c.6055G > A p.(Gly2019Ser) was tested with the Global Screening Array-24v2 (Illumina) in 942 population-based controls without PD diagnosis, matched by age, sex and area of residence with PD patients in MPBC cohort.

We searched PubMed for publications reporting genetic analyses of more than one dominant PD gene in the same series of PD patients and accessed The Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/) for allele frequencies of known pathogenic mutations in dominant PD genes [10,16].

3. Results

This study included a total of 2,206 PD patients from 7 Swedish sample collections at tertiary medical centers in Lund, Umeå, Stockholm, and Gothenburg, reflecting wide geographical distribution (Fig. 1). The majority of patients (85.4%) were recruited in population-based studies where all individuals diagnosed with PD in a certain geographical area were identified from the public health services' diagnosis registers and invited to participate (Table 1). Positive family history was defined slightly differently in the studies, but 12.1% of patients for whom such data was available reported a first-degree relative with PD, and an additional 9.5% a second-degree relative with PD (Table 1). Possible inclusion of the same individual in two studies was controlled by comparison of unique identifiers whenever possible. Samples were collected in the contributing studies between 1997 and 2017 (Table 1). In 2010, Sweden had a population of 9,415,570 inhabitants. Of these, 3,507,563 were aged 50 years or older, and among those, 81.9% were born in Sweden to parents born in Sweden, 14.6% were born abroad or had both parents born abroad, and 3.5% had one parent born abroad and one in Sweden.

In the 2,206 DNA samples, the call rate was 98.1% for *LRRK2* and *SNCA* point mutations and 98.8% for *SNCA* CNVs. MLPA analyses confirmed an *SNCA* duplication in one of eight samples with tentatively positive results from both digital PCR and TaqMan.

Known pathogenic point mutations were identified in 12 patients (Table 2), and were exclusively *LRRK2* p.(Gly2019Ser). This mutation was identified in patients from three different sample collections, corresponding to 0.54% of all patients included. Four of these mutation carriers had previously been reported [7] and were confirmed by both TaqMan and Sanger sequencing. Five of the 13 detected mutation carriers had a positive family history for PD. All mutation carriers were of Swedish origin. *LRRK2* p.(Gly2019Ser) was detected in 1 of 942 (0.11%) population-based controls from southern Sweden matched to the MPBC. The mutation carrier was of Swedish origin, as were 85.8% of the entire control cohort.

We identified 6 studies from 5 continents where series of PD patients were examined for mutations in more than one dominant PD gene [17–22] and these reported a frequency of *LRRK2* p.(Gly2019Ser)

Table 1
Case series included in this study.

Location (study, PI)	Number of samples from unique patients	Inclusion	Years of inclusion	Means of collecting clinical data	Mean age at onset/ diagnosis (years)	Self-reported positive family history: relatives with PD/Parkinsonism
Lund (MPBC)	658	Population-based/geographical diagnosis registry	2014–2017	Study visit to research nurse, record review	64.9 (AD)§	1st degree: 59 patients (9.0%) 2nd degree (only): 65 patients (9.9%)
Umeå (NYPUM)	643	Population-based/geographical diagnosis registry	2000–2016	Study visit to neurologist, record review	62.9 (AO)	1st degree: 69 patients (10.7%) 2nd degree (only): 59 patients (9.2%)
Stockholm (Parkinson_Karolinska)	361[a]	Population-based/geographical diagnosis registry	1997–2014	In conjunction to ordinary visit to neurology clinic	59.0 (AO)	1st degree: 53 patients (14.7%) 2nd degree (only): 23 patients (6.4%)
Gothenburg	228[a]	Service-based	2000–2012	Study visit to research nurse	57.0 (self- reported AO)	1st degree: 22 patients (9.6%) 2nd degree (only): 20 patients (8.8%)
Stockholm (BioPark)	165	Service-based	2013- ongoing	As part of regular outpatient visit	63.0 (AD)	1st degree: 31 patients (17.9%) 2nd degree: NA
Lund (PARLU)	127[b]	Population-based portion; portion patients with heredity	2008-ongoing	Study visit to neurologist/neurology registrar, record review	60.6 (AO)	1st degree: 41 patients (32.3%) 2nd degree (only): 13 patients (10.2%)
Stockholm (BPS)	24	Service-based	2012–2014	As part of regular outpatient visit	61.1 (AO)	1st degree: 2 patients (8.3%) 2nd degree (only): 2 patients (8.3%)
Total	**2,206**					

Patients were included in 7 individual studies characterized in this table.
NA, not available.
§ Based on information on 544 patients for whom these data were available. Average age at onset was 60.7 years for all those 1,383 patients for whom this data was available. Average age at diagnosis was 64.4 years for 717 additional patients.

[a] From these sample collections, 179 patients from Stockholm and 105 patients from Gothenburg had previously been analyzed for *LRRK2* p.(Gly2019Ser) mutations in a research study [7].

[b] All these had previously been examined for all *LRRK2* point mutations within an international multicenter study [3]. One patient from this series who had an *SNCA* p.Ala53Thr mutation [12] was not included in the present study.

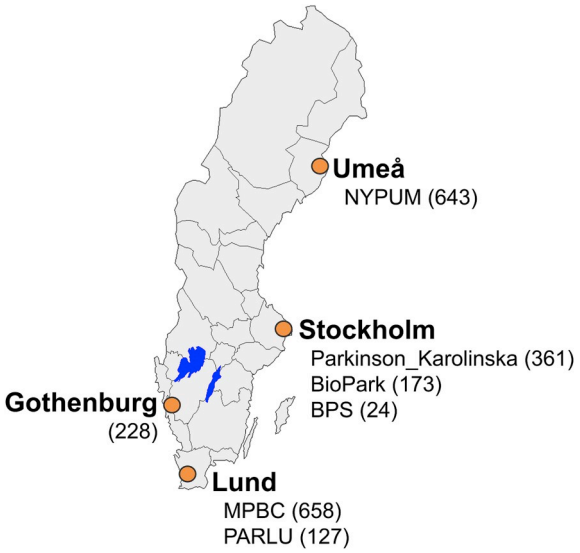

Fig. 1. The Swedish Parkinson Genetics Network. Map showing the locations and names of the seven contributing independent research studies. Figures represent the number of DNA samples from PD patients analyzed within this study.

between 0 and 4.3% (Supplementary Table 3).

Data from the gnomAD database was extracted for known pathogenic variants. There was information on 245,858 to 277,174 alleles for identified variants, with an allele frequency of 0.049% for *LRRK2* p.(Gly2019Ser), corresponding to a carrier frequency of 0.098%. Between populations, there were marked differences in the carrier frequency of this variant. By far the highest carrier frequency of *LRRK2* p.(Gly2019Ser), 1.63%, was observed among Ashkenazi Jewish population genotypes in gnomAD. This was 42 times higher than in genotypes from all other populations in gnomAD combined (0.039%). Carrier frequencies for all point mutations with well-established pathogenicity in all dominant PD genes taken together was 0.11% (Supplementary Table 4).

4. Discussion

Genetic screening of 2,206 Swedish PD patients for 8 mutations known to cause dominant PD identified mutations in only 13 (0.59%) individuals, while 21.6% of the patients had at least one first- or second-degree relative with PD. Of the 13 mutations, 12 were *LRRK2* p.(Gly2019Ser) and 1 was an *SNCA* duplication. *LRRK2* p.(Gly2019Ser) is known to have a markedly incomplete and varying penetrance [4,5] and was also found in 0.11% of population-based controls from one of our genotyped cohorts. *LRRK2* p.(Gly2019Ser) also represented the vast majority (90.4%) of known pathogenic mutations in the gnomAD datasets. Thus, *LRRK2* p.(Gly2019Ser) is the relatively most common, but the presently known mutations in dominant PD genes can only explain a minute fraction of PD in the population, and similarly only a small proportion of the familial aggregation of PD.

Strengths of this national multi-center study include that, based on prevalence estimates [23], more than 10% of the expected number of all PD patients in Sweden were examined, and that the vast majority (85.4%) of patients were included in population-based studies at geographically dispersed sites within the country. There were no restrictions regarding age at onset or at diagnosis, and most patients in our case series had late-onset PD with an average age of 60.7 years at onset, or 64.4 years at diagnosis, further emphasizing the representative nature of our samples.

The 8 variants were selected to include established causes for monogenic, dominantly inherited PD previously published in PD patients from Sweden: *SNCA* duplications and p.(Ala53Thr), *LRRK2* p.(Asn1437His) and p.(Gly2019Ser) [7,12,13,24], or from historically related populations in Norway, Denmark, United Kingdom, or Germany: *SNCA* p.(Ala30Pro), *LRRK2* p.(Arg1441His), p.(Tyr1699Cys) and p.(Ile2020Thr) [25,26].

We see additional strengths of our study in the fact that these 8 mutations were analyzed in the same patient series, allowing us to determine their overall burden in PD patients, and a high success rate of the genetic analyses, including the technically more difficult testing of *SNCA* CNVs. To our knowledge, this is the largest patient series tested for *SNCA* CNVs reported to date.

Founder effects may lead to marked differences in the frequency of variants between populations. For *LRRK2* p.(Gly2019Ser), there is a known South-to-North gradient in the European and Mediterranean region, and somewhat higher frequencies are encountered in southern Europe, for example 1.6% in a large case series from Italy [6,27]. The background population from where the patients in the present study were recruited can be very well defined based on Sweden's national population database. The population of Sweden includes a considerable percentage of individuals born in other countries, mostly in other Europe countries, followed by Asia. Since PD starting before age 50 is very unusual [28], we used population data from residents 50 years or older as a reference. In the Swedish population aged 50 years or older, 14.6% were born abroad or had both parents born abroad and an additional 3.5% had one parent born abroad. Information on ethnicity is not typically collected in Swedish health services and was not collected in most participating research studies, which may represent a limitation of our study. However, we consider it likely that a considerable proportion of patients in our series were of ethnically non-Swedish or non-European origin.

Another limitation of our study is that not all dominant pathogenic variants were analyzed, including the, in other populations, relatively more common variants *LRRK2* p.(Arg1441His), p.(Arg1441Cys) and *VPS35* p.(Asp620Asn). However, these had not been documented in Sweden or neighboring countries.

We found only three previous studies that analyzed both *SNCA* CNV and *LRRK2* p.(Gly2019Ser) in the same patient series, allowing for direct comparison of their frequency. These also showed that *LRRK2* p.(Gly2019Ser) is the most frequently encountered variant in dominant PD genes, followed by *SNCA* duplications.

The low prevalence of pathogenic mutations in our multi-center cohort when compared to some of the previous literature might indicate a marked selection bias, a publication bias, or reflect true differences in the presence of these mutations between populations. To address this question, we compared our results with the frequency of these mutations in the gnomAD dataset. Data included in gnomAD originate from a large number of original new generation sequencing studies, including studies on Alzheimer disease, migraine, and psychiatric disorders, but not on PD or other neurological or neurodegenerative disorders. We found that 0.11% of the individuals included in gnomAD carried one of the 5 most common *LRRK2* variants, almost exclusively *LRRK2* p.(Gly2019Ser), whereas none at all of the undoubtedly pathogenic *SNCA* point mutations were found. There was a marked 42-fold difference in the frequency of *LRRK2* p.(Gly2019Ser) in gnomAD between 1.63% in Ashkenazi Jews and 0.039% in all other ethnicities, confirming the presence of a relatively ancient founder in Mediterranean populations. *LRRK2* p.(Gly2019Ser) is also known to be common in Northern African populations but these are poorly represented in gnomAD.

We show that these *SNCA* and *LRRK2* mutations are very rare events, which may influence decisions about clinical genetic testing. Among 2,206 patients, only 12 carried *LRRK2* p.(Gly2019Ser), four of whom belonged to the 21.6% (478 patients) reporting positive family history. Thus, approximately 120 PD patients reporting one or more first- or second-degree relative(s) with PD needed to be tested to identify one *LRRK2* p.(Gly2019Ser) carrier. For *SNCA* CNV, we tested 2,206 patients to identify one carrier (0.045%), who had positive family

Table 2
PD patients with mutations in dominant PD genes.

Individual	Site (Study)	Mutation	Sex	AO	Age at inclusion	Pos. family history	Brady-kinesia	Rigi-dity	Tremor	RBD symptoms	Cognitive dysfunction	Ortho-statism	Comment
1906–1119	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	M	53 (AD)	59	Yes	Yes	Yes	No	No	No	No	Parent had dementia, other relative PD
1906–1767	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	F	50 (AD)	75	No	Yes	Yes	No	Yes	Yes	Yes	No self-reported family history of PD or AD
1906–1150	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	F	45 (AD)	49	Yes	Yes	Yes	No	No	No	No	Parent and grandparent had PD
1906–1211	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	M	59 (AD)	63	Yes	Yes	Yes	No	N.A.	No	No	Grandparent had PD
1906–1210	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	F	56 (AD)	63	No	Yes	Yes	Yes	N.A.	No	No	No self-reported family history of PD or AD
1906–1645	Lund (MPBC)	LRRK2 p.(Gly2019Ser)	M	64 (AD)	66	No	N.A.	Yes	Yes	No	No	No	No self-reported family history of PD or AD
PD1-A12	Stockholm (Parkinson_Karolinska)	LRRK2 p.(Gly2019Ser)	M	75	79	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Hemiparkinsonsism
PD2-E07	Stockholm (Parkinson_Karolinska)	LRRK2 p.(Gly2019Ser)	F	58	74	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–
PD2-H07	Stockholm (Parkinson_Karolinska)	LRRK2 p.(Gly2019Ser)	M	47	51	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Heart condition, has had a stroke
PD3-E09	Stockholm (Parkinson_Karolinska)	LRRK2 p.(Gly2019Ser)	M	53	58	Yes	N.A.	Yes	Yes	N.A.	N.A.	N.A.	–
PD4-A11	Stockholm (Parkinson_Karolinska)	LRRK2 p.(Gly2019Ser)	M	54	56	No	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	–
10793	Umeå (NYPUM)	LRRK2 p.(Gly2019Ser)	F	48	60	No	Y	Y	Y	N	N	Y	–
1906-1750	Lund (MPBC)	*SNCA* duplication	F	52	54	Yes	Y	Y	N	Y	Y	Y	*

This table summarizes the clinical data on the 13 patients carrying one of the known pathogenic mutations tested. N.A., not available. *This patient belongs to the Swedish Lister Family, a large kindred with *SNCA* multiplications [14]. Her carrier status was known from the PARLU study, why her DNA was excluded from the present analyses. She turned out to be included in MPBC as well.

history. All other genetic variants tested were not found, indicating they have lower frequencies. A recent Australian study examined 137 probands from multi-incident families with 3 or more members with PD by whole exome sequencing (WES) and identified 3 *LRRK2* p.(Gly2019Ser) and 2 *VPS35* p.(Asp620Asn) carriers [21]. Thus, 27 patients from such multi-incident families were examined by WES per one identified mutation carrier. In most populations, genetic testing for dominant PD may be indicated under specific circumstances and in individual patients, and a positive result may become more likely with an increasing number of affected family members.

The genetic architecture of PD is complex, and an interplay of more than one genetic factor such as in digenic or oligogenic inheritance is likely [29,30]. Thus, future research into the genetic etiology of (familial) PD should not be limited to single mutations or genes. A steadily expanding number of WES datasets from PD patients may make it possible to explore complex interactions.

Authors' roles

Andreas Puschmann: Initiative to, design and conceptualization of the study; Overall study co-ordination; Drafting and revising the manuscript for intellectual content; Analysis and interpretation of the data, Major role in the acquisition of data (inclusion of patients in PARLU study, providing samples from PARLU study, coordinating PARLU study; Steering group member for MPBC samples collection; literature review); Acquisition of funding; Supervision of personnel.

Itzia Jimenez-Ferrer: Drafting of manuscript portion and revising the manuscript for intellectual content, Analysis or interpretation of data, Major role in the acquisition of data (genetic analyses).

Elin Lundblad-Andersson: Drafting of manuscript portion and revising the manuscript for intellectual content, Analysis or interpretation of data, Major role in the acquisition of data (genetic analyses).

Emma Mårtensson: Drafting of manuscript portion and revising the manuscript for intellectual content, Analysis or interpretation of data, Major role in the acquisition of data (performing genetic analyses).

Oskar Hansson: Revising the manuscript for intellectual content; Initiating and responsibility for MPBC sample collection; Steering group member of MPBC; Acquisition of funding; Supervision of personnel.

Per Odin: Revising the manuscript for intellectual content; Steering group member for MPBC samples collection.

Håkan Widner: Revising the manuscript for intellectual content; Steering group member for MPBC samples collection.

Kajsa Brolin: Drafting of manuscript portion and revising the manuscript for intellectual content; Major role in the acquisition of data (retrieving clinical data from MPBC patients and data from NGS databases).

Ropafadzo Mzezewa: Revising the manuscript for intellectual content; Major role in the acquisition of data (genetic analyses).

Jonas Kristensen: Revising the manuscript for intellectual content; Major role in the acquisition of data (genetic analyses).

Maria Soller: Revising the manuscript for intellectual content; study organization (organization of genetic analyses); Supervision of personnel.

Emil Ygland Rödström: Drafting of manuscript portion and revising the manuscript for intellectual content (retrieving data from NGS databases and from previous studies of PD patient series, revising tables for accuracy).

Owen A. Ross: Revising the manuscript for intellectual content; Study design (selection of genetic variants to test).

Mathias Toft: Revising the manuscript for intellectual content; Providing positive samples for genetic analyses.

Guido J. Breedveld: Drafting of manuscript portion and revising the manuscript for intellectual content; Performing genetic analyses (SNCA copy number analysis).

Vincenzo Bonifati: Drafting of manuscript portion and revising the manuscript for intellectual content; Acquisition of funding for genetic analyses (SNCA copy number analysis).

Lovisa Brodin: Revising the manuscript for intellectual content; Providing samples from BioPark study.

Anna Zettergren: Revising the manuscript for intellectual content; Providing samples from Gothenburg study.

Olof Sydow: Revising the manuscript for intellectual content; Inclusion of patients in Parkinson_Karolinska study.

Jan Linder: Revising the manuscript for intellectual content; Inclusion of patients in NYPUM study.

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Andrea Carmine Belin: Drafting of manuscript portion and revising the manuscript for intellectual content; Major role in the acquisition of data (inclusion of patients in Parkinson_Karolinska study, providing samples from Parkinson_Karolinska study, coordinating Parkinson_Karolinska study); Acquisition of funding.

Lars Forsgren#: Drafting of manuscript portion and revising the manuscript for intellectual content; Major role in the acquisition of data (inclusion of patients in NYPUM study, providing samples from NYPUM study, coordinating NYPUM study); Acquisition of funding.

Maria Swanberg#: Revising the manuscript for intellectual content; Major role in the acquisition of data (providing samples from MPBC study, coordinating MPBC study, coordinating genotyping performed at the Translational Neurogenetics Unit); Supervision of personnel; Acquisition of funding.

#These authors have contributed equally.

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