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

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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 ethnicities.
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 Sweden, only a small number of patients have been identified with mutations in 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/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.A., E.M., J.K., M.S.), and/or at the Translational Neurogenetics Unit, Lund University (I.F., R.M., M.Sw.).

Seven point mutations in SNCA (NM_000345.3) and LRRK2 (NM_198758.3) 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), rs34993736; 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 (CFX96m 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 unqueenching of fluorescent probes for SNCA (TaqMan Copy Number Assay ID: Hs03506784_cn) and the ribonuclease P RNA component H1 gene RPPH1 (TaqMan assay no. 44033262) 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.

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

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.

* 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.
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 Swedish 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>
<thead>
<tr>
<th>Individual</th>
<th>Site (Study)</th>
<th>Mutation</th>
<th>Sex</th>
<th>AO</th>
<th>Age at inclusion</th>
<th>Pos. family history</th>
<th>Brady-kinesia</th>
<th>Rigi-dity</th>
<th>Tremor symptoms</th>
<th>RBD symptoms</th>
<th>Cognitive dysfunction</th>
<th>Orthostatism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1906–1119</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>53</td>
<td>59</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Parent had dementia, other relative PD</td>
</tr>
<tr>
<td>1906–1767</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>F</td>
<td>50</td>
<td>75</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No self-reported family history of PD or AD</td>
</tr>
<tr>
<td>1906–1150</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>45</td>
<td>49</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Parent and grandparent had PD</td>
</tr>
<tr>
<td>1906–1211</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>F</td>
<td>59</td>
<td>63</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Grandparent had PD</td>
</tr>
<tr>
<td>1906–1210</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>56</td>
<td>63</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N.A.</td>
<td>No</td>
<td>No</td>
<td>No self-reported family history of PD or AD</td>
</tr>
<tr>
<td>1906–1645</td>
<td>Lund (MPBC)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>64</td>
<td>66</td>
<td>No</td>
<td>N.A.</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No self-reported family history of PD or AD</td>
</tr>
<tr>
<td>PD1-A12</td>
<td>Stockholm (Parkinson_Karolinska)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>75</td>
<td>79</td>
<td>No</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A</td>
<td>N.A.</td>
<td>Hemiparkinsonism</td>
</tr>
<tr>
<td>PD2-B07</td>
<td>Stockholm (Parkinson_Karolinska)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>F</td>
<td>58</td>
<td>74</td>
<td>No</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A</td>
<td>N.A.</td>
<td>--</td>
</tr>
<tr>
<td>PD2-B07</td>
<td>Stockholm (Parkinson_Karolinska)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>47</td>
<td>51</td>
<td>No</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A</td>
<td>N.A.</td>
<td>Heart condition, has had a stroke</td>
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<tr>
<td>PD1-B09</td>
<td>Stockholm (Parkinson_Karolinska)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>53</td>
<td>58</td>
<td>Yes</td>
<td>N.A.</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>N.A</td>
<td>N.A.</td>
<td>--</td>
</tr>
<tr>
<td>PD4-A11</td>
<td>Stockholm (Parkinson_Karolinska)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>M</td>
<td>54</td>
<td>56</td>
<td>No</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A</td>
<td>N.A.</td>
<td>--</td>
</tr>
<tr>
<td>10793</td>
<td>Umeå (NYPUM)</td>
<td>LRRK2 p. (Gly2019Ser)</td>
<td>F</td>
<td>48</td>
<td>60</td>
<td>No</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>--</td>
</tr>
<tr>
<td>1906–1750</td>
<td>Lund (MPBC)</td>
<td>SNC duplication</td>
<td>F</td>
<td>52</td>
<td>54</td>
<td>Yes</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>*</td>
</tr>
</tbody>
</table>

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 SNC duplication [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 Rödstrom: 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.

Karim Wirdefeldt: Drafting of manuscript portion and revising the manuscript for intellectual content; Major role in the acquisition of data (inclusion of patients in BioPark study, providing samples from BioPark study, coordinating BPS study).

Per Svenningsson: Drafting of manuscript portion and revising the manuscript for intellectual content; Major role in the acquisition of data (inclusion of patients in BioPark study, providing samples from Gothenburg study, coordinating Gothenburg study); Acquisition of funding.

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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