

Family History in Parkinson's Disease: A National Cross-Sectional Study

Federica Arienti, MD,^{1,2}  Giovanni Casazza, PhD,^{3,4} Giulia Franco, MD, PhD,^{1,2} Giulia Lazzeri, MD,^{2,5}  Edoardo Monfrini, MD, PhD,^{1,2} Alessandro Di Maio, MD,^{1,2} Roberto Erro, MD, PhD,⁶  Paolo Barone, MD, PhD,⁶ Filippo Tamma, MD,⁷ Elena Caputo, MD,⁷ Maria Antonietta Volontè, MD,⁸ Laura Cacciaguerra, MD, PhD,⁸ Andrea Pilotto, MD,⁹  Alessandro Padovani, MD, PhD,⁹ Cristoforo Comi, MD, PhD,¹⁰ Luca Magistrelli, MD, PhD,⁵  Franco Valzania, MD,¹¹ Francesco Cavallieri, MD, PhD,¹¹  Laura Avanzino, MD, PhD,^{12,13}  Roberta Marchese, MD,¹³ Mariachiara Sensi, MD, PhD,¹⁴  Giorgia Carroli, MD,¹⁴ Roberto Eleopra, MD,¹⁵ Roberto Cilia, MD,¹⁵  Francesca Spagnolo, MD, PhD,¹⁶ Alessandro Tessitore, MD, PhD,¹⁷ Rosa De Micco, MD, PhD,¹⁷  Roberto Ceravolo, MD,¹⁸  Giovanni Palermo, MD, PhD,¹⁸ Maria Chiara Malaguti, MD,¹⁹ Leonardo Lopiano, MD, PhD,^{20,21} Pierluigi Tocco, MD,²² Chiara Sorbera, MD, PhD,²³ Michele Tinazzi, MD, PhD,²⁴  Andrea Ciammola, MD,²⁵ Donatella Ottaviani, MD, PhD,²⁶ Enza Maria Valente, MD, PhD,^{27,28}  Alberto Albanese, MD,²⁹  Fabio Blandini, MD, PhD,⁴ Margherita Canesi, MD,³⁰ Angelo Antonini, MD, PhD,³¹  Miryam Carecchio, MD, PhD,³¹ Vincenza Fetoni, MD,³² Carlo Colosimo, MD,³³ Daniele Volpe, MD,³⁴ Nicola Tambasco, MD, PhD,³⁵  Giovanni Cossu, MD,³⁶ Mario Zappia, MD,³⁷  Italian Study Group on Family History in PD, and Alessio Di Fonzo, MD, PhD,^{1*} 

Abstract: Background: Family history of Parkinson's disease (PD) is a common finding in PD patients. However, a few studies have systematically examined this aspect.

Objectives: We investigated the family history of PD patients, comparing demographic and clinical features between familial PD (fPD) and sporadic PD (SPD).

Methods: A cross-sectional study enrolling 2035 PD patients was conducted in 28 Italian centers. Clinical data and family history up to the third degree of kinship were collected.

¹Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy; ²Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; ³Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy; ⁴Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ⁵Gaetano Pini-CTO, Parkinson Institute, Milan, Italy; ⁶Neuroscience Section, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Baronissi (SA), Italy; ⁷Department of Neurology, "F. Miuili" General Hospital, Acquaviva delle Fonti, Italy; ⁸Department of Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy; ⁹Neurology Unit and Neurobiorepository and Laboratory of Advanced Biological Markers, Department of Clinical and Experimental Sciences, University of Brescia, and Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia Hospital, Brescia, Italy; ¹⁰Department of Translational Medicine, Section of Neurology, University of Piemonte Orientale, Novara, Italy; ¹¹Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; ¹²Department of Experimental Medicine, Section of Human Physiology, University of Genoa, Genoa, Italy; ¹³IRCCS Ospedale Policlinico San Martino—UOC Genetica Medica, Genoa, Italy; ¹⁴Department of Neuroscience and Rehabilitation, Azienda Ospedaliera-Universitaria S. Anna, Ferrara, Italy; ¹⁵Fondazione IRCCS Istituto Neurologico Carlo Besta, Department of Clinical Neurosciences, Movement Disorders Unit, Milan, Italy; ¹⁶Neurological Department, A. Perrino's Hospital, Brindisi, Italy; ¹⁷Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Caserta, Italy; ¹⁸Unit of Neurology, Department of Clinical and Experimental Medicine Center for Neurodegenerative Diseases—Parkinson's Disease and Movement Disorders, University of Pisa, Pisa, Italy; ¹⁹Neurology Unit, Trento Hospital, Azienda Provinciale per i Servizi Sanitari (APSS) di Trento, Trento, Italy; ²⁰Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy; ²¹Neurology 2 Unit, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy; ²²Neurology and Stroke Unit, Pescara Hospital, Pescara, Italy; ²³Neurorehabilitation Unit IRCCS Centro Neurolesi "Bonino Pulejo", Messina, Messina, Italy; ²⁴Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy; ²⁵Department of Neurology and Laboratory of Neuroscience, Istituto Auxologico Italiano IRCCS, Milan, Italy; ²⁶Neurology Unit, Rovereto Hospital, Azienda Provinciale per i Servizi Sanitari (APSS) di Trento, Trento, Italy; ²⁷Department of Molecular Medicine, University of Pavia, Pavia, Italy; ²⁸Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy; ²⁹Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Italy; ³⁰Department of Parkinson's Disease, Movement Disorders and Brain Injury Rehabilitation, Moriggi Pelascini Hospital, Gravedona, Italy; ³¹Parkinson and Movement Disorders Unit, Center for Neurodegenerative Diseases (CENSE), Department of Neuroscience, University of Padua, Padua, Italy; ³²Neurology Department, ASST Fatebenefratelli Sacco, Milan, Italy; ³³Department of Neurology, Santa Maria Hospital, Terni, Italy; ³⁴Department of Neurorehabilitation, Parkinson's Disease Excellence Center, Casa di Cura Villa Margherita via Costacolonna n 1 Arcagnano, Vicenza, Italy; ³⁵Movement Disorders Center, Neurology Department, Perugia General Hospital and University of Perugia, Perugia, Italy; ³⁶Department of Neuroscience, Brotzu Hospital, Cagliari, Italy; ³⁷Department GF Ingrassia, University of Catania, Catania, Italy

*Correspondence to: Dr. Alessio Di Fonzo, Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Neurology Unit, Via Francesco Sforza, 35, 20122 Milan, Italy; E-mail: alessio.difonzo@policlinico.mi.it

Keywords: familial and sporadic Parkinson's disease, family history, hyposmia, cognitive impairment, depression, bipolar disorder.

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Results: Family history of PD was determined in 21.9% of patients. fPD patients had earlier age at onset than sporadic patients. No relevant differences in the prevalence of motor and nonmotor symptoms were detected. Family history of mood disorders resulted more prevalently in the fPD group.

Conclusions: fPD was found to recur more frequently than previously reported. Family history collection beyond the core family is essential to discover disease clusters and identify novel risk factors for PD.

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by the presence of bradykinesia, variably associated with resting tremor, muscle rigidity, and postural instability. Concerning its controversial etiopathology, both genetic and environmental factors are likely involved.¹⁻³

Positive family history for PD is an established risk factor for the development of the disease, especially in first-degree relatives, whose risk for the disease is estimated to increase by 2- to 3-fold.^{4,5} Previous studies reported familial recurrence of PD in 5% to 15% of patients.^{6,7}

This study aimed to analyze the family history of PD patients up to the third degree of kinship, assessing the frequency of familial forms of PD and comparing demographic and clinical features between familial (fPD) and sporadic (sPD) patients. The prevalence of other neurological and psychiatric disorders across family members was also assessed.

Patients and Methods

This is a cross-sectional study performed in 28 Parkinson's disease and movement disorders centers, located in 14 Italian regions.

Patients were consecutively recruited from outpatient clinics during a 30-month period, from April 1, 2020, to November 30, 2021.

The following inclusion criteria were applied to establish patient eligibility:

- Confirmed diagnosis of PD made by a movement disorder specialist, according to the Movement Disorder Society clinical diagnostic criteria⁴
- Signed informed consent to participate in the study
- Age over 18 years at the time of assessment

Exclusion criteria were defined as follows:

- Secondary or atypical parkinsonism
- Lack of sufficiently comprehensive biographical, clinical and anamnestic information

All data were entered into an electronic database. For each patient, family history for PD, essential tremor (ET), cognitive impairment, and major depressive and bipolar disorders was assessed up to the third degree of kinship using a structured family history interview.

The occurrence of one of the aforementioned conditions in PD family members was classified as follows:

- Certain, if the disease was diagnosed by a neurologist or a psychiatrist for what concerns movement disorders and psychiatric conditions/mood disorders, respectively

- Possible, if the disease was reported by patients or caregivers without formal assessment by a physician
- Negative, if the disease never occurred in the family
- Unknown, if data on family history were incomplete/missing (eg, in the case of adoption, early death, abandoned)

Clinical and genetic data were obtained through neurological examination and local databases. Descriptive statistic was employed to characterize the population demographics. Categorical variables have been reported as count (percentage) and continuous variables as mean (standard deviation). Statistical comparisons between groups were performed using Fisher's exact test for categorical variables and Wilcoxon 2-sample test for continuous variables. Statistical significance was set at the $\alpha = 0.05$ level, 2 sided. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

The entire study population was considered for demographic and epidemiological analyses. Only patients with certain (fPD) or negative (sPD) PD family history were included in comparison analyses.

Results

Family History for PD and Other Neuropsychiatric Disorders in PD Patients

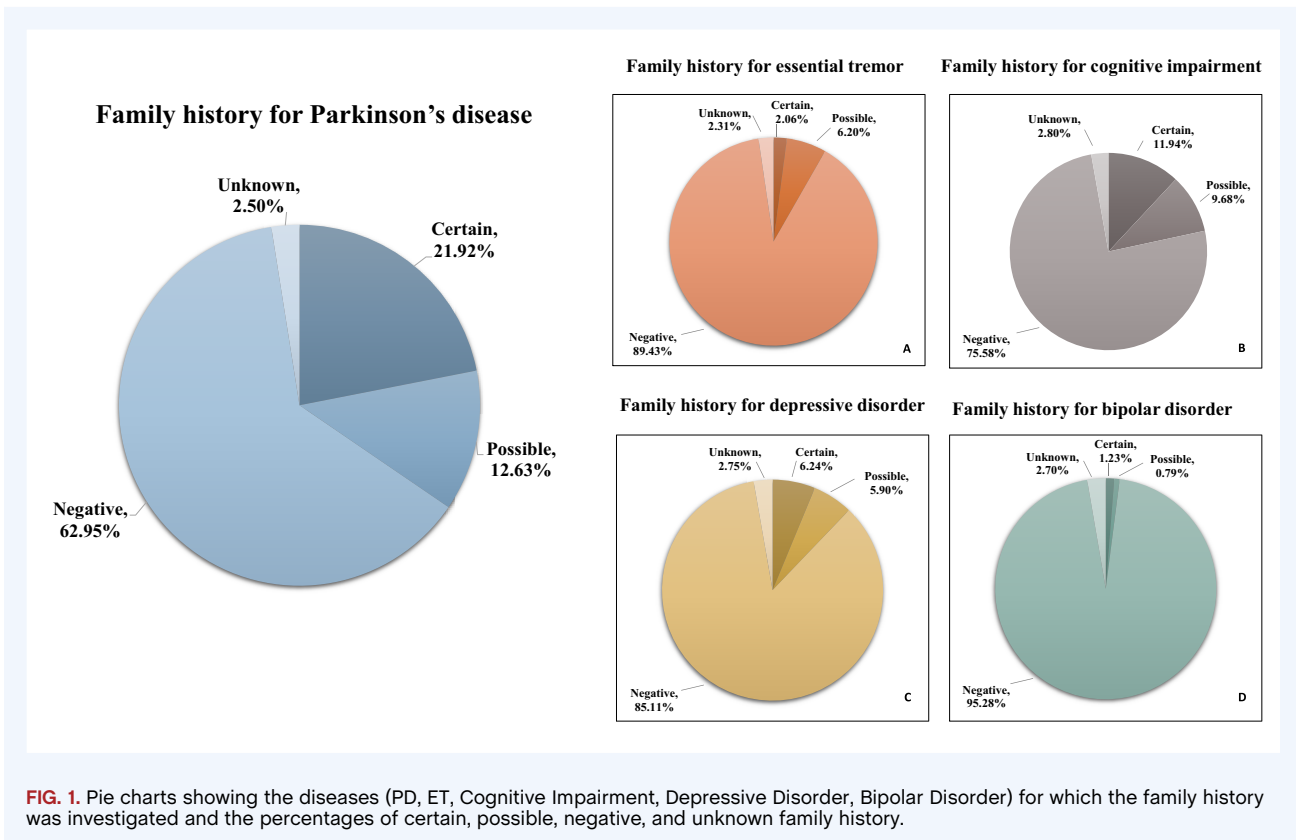
According to inclusion/exclusion criteria, 2035 PD patients were included in the study.

A male predominance was observed, with a male-to-female ratio of 1.5:1.0. The mean age at evaluation was 68.9 ± 10.6 years, the mean age at onset of motor symptoms was 60.2 ± 11.5 years, and the average disease duration was 8.7 ± 5.9 years.

A family history of any degree for PD was reported by 34.5% of PD patients ($n = 703$, certain plus possible). However, a formal diagnosis of PD could be demonstrated in the relatives of 21.9% of cases ($n = 446$, certain) (Fig. 1).

Considering PD patients with certain or possible family history for PD, 67.9% (477/703) reported at least 1 first-degree affected relative, whereas 32.1% (226/703) described only second- or third-degree affected family members.

As concerns other neurological and psychiatric disorders, 11.9% ($n = 243$) of PD patients reported certain family history for cognitive



impairment, 2% ($n = 42$) for ET, and 6.2% ($n = 127$) and 1.2% ($n = 25$) for depression and bipolar disorders, respectively (Fig. 1A–D). The inclusion of possible cases in the estimation of prevalence significantly increased numbers as follows: cognitive impairment = 21.6% ($n = 440$), ET = 8.2% ($n = 168$), depression = 12.1% ($n = 247$), and bipolar disorder = 2% ($n = 41$).

Comparison between fPD and sPD

No differences in mean age and sex distribution between fPD ($n = 446$) and sPD ($n = 1281$) groups were observed. The mean age at onset was significantly lower in fPD patients (58.5 ± 11.5 years) than in sPD (60.8 ± 11.5 years) ($P = 0.0001$), and mean disease duration was longer in the fPD group (9.6 years) than in the sPD group (8.4 years) ($P = 0.0002$). No relevant difference between the 2 groups in the modified Hoehn and Yahr Staging Scale scores corrected for disease duration was observed.

The distribution of motor and nonmotor symptoms between fPD and sPD was similar, except for hyposmia that resulted more frequently in the fPD group (Table 1).

Family history of depressive disorder (9.8% vs. 5.7%, $P = 0.0058$) was more common in fPD. A similar but not significant trend was observed for ET (3.7% vs. 2.0%, $P = 0.0647$), whereas no differences were observed in the recurrence of cognitive and bipolar disorders.

Genetics

Genetic testing was performed in 21.8% (443/2035) of the patients. In all cases a minimal gene set (ie, *SNCA*, *LRRK2*, *GBA1*, *PRKN*, and *PINK1*, including relevant dosage assays) was analyzed.

Considering the 372 subjects tested with certain positive or negative family history, a positive genetic result was more frequent in fPD (55/151, 36.4%) than in sPD (57/221, 25.8%) ($P = 0.0295$). The prevalence of pathogenic variants in the most common PD genes (*GBA1*, *LRRK2*, and *PRKN*) did not differ between sPD and fPD patients (Table S1). Most of the enrolled patients were not genetically tested, thus precluding further analyses and possibly enriching the rate of positive results by having selected more likely genetic cases (eg, due to family history, clinical characteristics or geographical origin).

Discussion

The frequency of family history of PD is known to be higher among PD cases than the general population.^{5,6} Previous studies reported that about 10% to 15% of PD patients have at least 1 affected relative.^{7,8} In this study, more than one-third of PD patients (34.5%) presented a positive family history for PD (21.9% when considering only certain cases, thus eliminating the limitation due to the anamnestic report of possible cases). The

TABLE 1 Comparison of clinical characteristics between patients with fPD and sPD

	fPD (n = 446)	sPD (n = 1281)	Statistical significance
Motor symptoms			
Rest tremor, % (n)	68.6 (306)	67.2 (861)	<i>P</i> = 0.5977
Rigidity, % (n)	86.1 (384)	85.1 (1090)	<i>P</i> = 0.6413
Postural instability, % (n)	24.0 (107)	25.3 (324)	<i>P</i> = 0.6116
Freezing, % (n)	20.4 (91)	17.4 (223)	<i>P</i> = 0.1755
Dystonia, % (n)	12.6 (56)	11.0 (141)	<i>P</i> = 0.3874
Pisa syndrome, % (n)	7.6 (34)	8.1 (104)	<i>P</i> = 0.8393
Camptocormia, % (n)	21.8 (97)	22.2 (284)	<i>P</i> = 0.8946
Nonmotor symptoms			
Hyposmia, % (n)	42.6 (190)	35.4 (453)	<i>P</i> = 0.0075
Constipation, % (n)	53.4 (238)	49.6 (635)	<i>P</i> = 0.1698
Orthostatic hypotension, % (n)	16.1 (72)	17.1 (219)	<i>P</i> = 0.6603
Urinary symptoms, % (n)	41.3 (184)	39.0 (499)	<i>P</i> = 0.3994
Sialorrhoea, % (n)	15.9 (71)	13.5 (173)	<i>P</i> = 0.2075
Rem behavior disorder, % (n)	46.0 (205)	43.3 (555)	<i>P</i> = 0.3467
Depression, % (n)	31.6 (141)	31.2 (399)	<i>P</i> = 0.8589
Bipolar disorder, % (n)	0.9 (4)	0.6 (8)	<i>P</i> = 0.5195
Cognitive decline, % (n)	13.5 (60)	16.6 (212)	<i>P</i> = 0.1314
Psychosis, % (n)	8.5 (38)	10.2 (131)	<i>P</i> = 0.3105
Anxiety, % (n)	33.0 (147)	29.4 (377)	<i>P</i> = 0.1692
Pain, % (n)	23.8 (106)	19.8 (253)	<i>P</i> = 0.0781
Family history of neuropsychiatric disorders			
Essential tremor, % (n)	3.7 (15)	2.0 (24)	<i>P</i> = 0.0647
Cognitive impairment, % (n)	15.6 (61)	13.8 (160)	<i>P</i> = 0.4027
Depression, % (n)	9.8 (40)	5.7 (68)	<i>P</i> = 0.0058
Bipolar disorder, % (n)	1.4 (6)	1.3 (16)	<i>P</i> = 0.8082

Statistically significant differences are indicated in blue, whereas trends of clinical interest are highlighted in gray. Abbreviations: fPD, familial Parkinson's disease; Rem, rapid eye movements; sPD, sporadic Parkinson's disease.

higher rate of positive family history encountered may suggest either a major role played by genetic factors in the Italian PD population or a possible underestimation in previous studies. A plausible explanation may be the limitation of data collection to first-degree relatives. Interestingly, a remarkable 32.1% of PD patients reported only second- or third-degree affected family members, which should prompt clinicians to investigate the family history more thoroughly.

As a matter of fact, given the incidence of PD in the general population, the presence of more than 1 family member affected may not be related to genetic factors.

In line with previous studies,^{6,9,10} fPD exhibited younger age at onset. This observation could be due to a higher prevalence of genetic forms in fPD or to an earlier recognition of PD symptoms by patients with affected relatives.¹¹

No major differences in motor phenotype between fPD and sPD were observed, confirming previous observations,^{9,12} with a few exceptions.¹⁰

Among nonmotor features, hyposmia was more represented in the fPD group. A clear explanation of this finding is still elusive. The higher prevalence may be due to PD genetic risk factors predisposing also to PD-related hyposmia in familial cases.¹³ However, confounding factors (eg, cigarette smoking, allergies, drugs) that were not collected in this study may also play a role.

We then investigated the occurrence of neurological and psychiatric features in relatives of PD patients. To this aim, we collected data on whether PD relatives had a diagnosis of disorders previously associated with PD (ie, ET, bipolar disorder, and depression) or presented clinical features (ie, tremor, cognitive

impairment, and mood disorders), which may occur in prodromal PD.

A certain diagnosis of ET was present in family members of 2% of the patients, whereas in 6.2% the diagnosis of ET was reported as possible. The remarkable difference between the certain and possible ET diagnoses is likely reflecting the uncertainty in categorizing tremor in terms of diagnosis and phenomenology. Indeed, the coexistence of PD and ET has been reported in PD patients, and ET was consistently found with a higher prevalence in family members of PD patients compared to those of controls.¹⁴

However, the relationship between ET and PD remains controversial, and most studies failed to find a significant connection.¹⁵ These observations should prompt the collection of family history of ET in PD patients, encouraging further assessments and clinical studies to better understand these associations.

A diagnosis of cognitive impairment was reported from 12% (certain) to 21% (certain + possible) of PD families. This prevalence did not include relatives affected by PD dementia. A precise characterization of the cognitive disorders (Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, etc.) was often not retrievable due to missing anamnestic data. Such a prevalence of cognitive impairment in PD family members may be explained by shared molecular mechanisms between PD and other neurodegenerative disorders, as demonstrated by the presence of common genetic risk factors (ie, *GBA1*, *C9ORF72*, *MAPT*, *PSEN1*).^{16–20}

Depression and anxiety were referred in 32% and 31% of PD patients, respectively (Table 1). This finding is higher compared to the reported prevalence of such symptoms in the Italian population (3%–6% and 2%–5%, respectively).^{21,22} Notably, bipolar disorder, which has been proposed as a risk factor for PD, was quite rare in this cohort, occurring in 0.7% of patients.^{23,24} Finally, a higher prevalence of mood disorders was observed in family members of fPD compared to sPD relatives. This observation may suggest a role of genetic factors in the predisposition of mood disorders, likely representing prodromal symptoms of PD.

In conclusion, PD patients have a higher prevalence of family members affected than previously reported, reaching up to one-third of cases after recording information on second- and third-degree relatives. This observation should stimulate further studies evaluating the risk of PD in family members to improve the counseling in PD patients and their families. Moreover, the identification of familial clusters will help to dissect the genetic and nongenetic contributions to the pathogenesis of PD and other neurodegenerative disorders.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

F.A.: 1A, 1B, 1C, 2A, 2B, 3A

G.C.: 2A, 2B, 2C

G.F., G.L., E.M., A.D.M.: 1C, 2A, 3B, 3B

A.D.F.: 1A, 2C, 3B

C.C., L.L., M.Z., A.R., F.S., P.D.M., N.T., A.A., A.A., M.C., L.A., R.M., F.D.B., T.B.M., M.C., A.R., R.C., G.P., A.F., A.C., N.T., E.M., G.C., L.M., C.C., E.C., R.C., R.E., P.B., M.P., C.S., V.F., C.L., M.C.M., M.P., C.L., O.D., R.D.G., A.P., A.P., A.L., A.I., M.C.S., G.C., A.B., C.S., G.D.L., A.B., P.N., F.T., E.C., P.V.M., S.T., A.T., R.D.M., S.A., M.T., I.D., S.O., P.T., F.D.B.; A.D'A.; F.V., F.C., G.T., V.F., M.A.V., L.C., S.G., G.D.N., D.V., M.Z., E.M.V., F.B.: 1C, 3B

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Italian Study Group on Family History in PD:

- M. Picillo (Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana,” Neuroscience Section, University of Salerno, Baronissi [SA], Italy)
- C. Sorrentino (Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana,” Neuroscience Section, University of Salerno, Baronissi [SA], Italy)
- P.V. Mancino (Department of Neurology, “F. Miulli” General Hospital, Acquaviva delle Fonti, Italy)
- S. Tagliente (Department of Neurology, “F. Miulli” General Hospital, Acquaviva delle Fonti, Italy)
- S. Galantucci (Department of Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy)
- G. Di Napoli (Department of Neurology, IRCCS San Raffaele Scientific Institute, Milan, Italy)
- A. Luppini (Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, and Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia Hospital, Italy Brescia, Italy)
- A. Imarisio (Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, and Department of Continuity of Care and Frailty, ASST Spedali Civili Brescia Hospital, Italy Brescia, Italy)
- E. Contaldi (Department of Translational Medicine, Section of Neurology, University of Piemonte Orientale, Novara, Italy)
- R. Cantello (Department of Translational Medicine, Section of Neurology, University of Piemonte Orientale, Novara, Italy)
- G. Toschi (Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia 42124, Italy)

- V. Fioravanti (Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia 42124, Italy)
- F. Di Blasio (IRCCS Ospedale Policlinico San Martino—UOC Genetica Medica, Largo R. Benzi 10, 16132 Genova, Italy)
- T. Benzi Markushi (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Largo P. Daneo 3, 16132 Genova, Italy)
- A. Braccia (Department of Neuroscience and Rehabilitation, Azienda Ospedaliera-Universitaria S. Anna, Ferrara)
- A. Rini (Neurological Department, A. Perrino's Hospital, Brindisi, Italy)
- P. De Marco (Neurological Department, A. Perrino's Hospital, Brindisi, Italy)
- S. Aramini (Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli")
- A. Francesconi (Center for Neurodegenerative Diseases—Parkinson's Disease and Movement Disorders, Unit of Neurology, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy)
- M. Pellegrini (Neurology Unit, Trento Hospital, Azienda Provinciale per i Servizi Sanitari [APSS] di Trento, Trento 38122, Italy)
- C. Longo (Neurology Unit, Trento Hospital, Azienda Provinciale per i Servizi Sanitari [APSS] di Trento, Trento 38122, Italy)
- M. Zibetti (Department of Neuroscience "Rita Levi Montalcini," University of Turin, Via Cherasco 15, 10126 Turin, Italy; Neurology 2 Unit, A.O.U. Città della Salute e della Scienza di Torino, Corso Bramante 88, 10126 Turin, Italy)
- C. Ledda (Department of Neuroscience "Rita Levi Montalcini," University of Turin, Via Cherasco 15, 10126 Turin, Italy; Neurology 2 Unit, A.O.U. Città della Salute e della Scienza di Torino, Corso Bramante 88, 10126 Turin, Italy)
- F. Di Blasio (Neurology and Stroke Unit, Pescara Hospital, Pescara, Italy)
- A. D'Andreagiovanni (Neurology and Stroke Unit, Pescara Hospital, Pescara, Italy)
- G. Di Lorenzo (Neurorehabilitation Unit IRCCS Centro Neurolesi "Bonino Pulejo," Messina, Italy)
- A. Brigandi (Neurorehabilitation Unit IRCCS Centro Neurolesi "Bonino Pulejo," Messina, Italy)
- I. Divico (Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy)
- S. Ottaviani (Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy)
- N. Ticozzi (Department of Neurology and Laboratory of Neuroscience, Istituto Auxologico Italiano IRCCS, Milan, Italy)
- R. Di Giacomo (Neurology Unit, Rovereto Hospital, Azienda Provinciale per i Servizi Sanitari [APSS] di Trento, Trento, Italy)
- A. Ranghetti (Department of Parkinson's Disease, Movement Disorders and Brain Injury Rehabilitation, Moriggia Pelascini Hospital, Gravedona, Italy)
- E. Manfroi (Department of Neurology, Santa Maria University Hospital, Terni, Italy)
- P. Nigro (Movement Disorders Center, Neurology Department, Perugia General Hospital and University of Perugia, Perugia, Italy)

Disclosures

Ethical Compliance Statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Milan (Comitato Etico Milano Area 2, parere 1106_2019). Written informed consent was obtained for each patient participating in this work. All authors have read and complied with the journal's ethical publication guidelines. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Distribution of GBA1, LRRK2 and PARK2 mutations in fPD and sPD with positive results in genetics analysis.