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Familial Aggregation of Parkinson's Disease in a Multiethnic Community-Based Case-Control Study

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Abstract

To assess the familial aggregation of Parkinson's disease (PD), we compared the cumulative incidence of PD among first-degree relatives of PD cases and controls. We identified newly diagnosed patients with PD (n=573) during 1994–1995 within Kaiser Permanente Medical Care Program (KPMPC) of Northern California and recruited 496 cases (87%) for the case-control study. Of 720 eligible controls matched by birth year and sex to cases, 541 (75%) agreed to participate. Information on family history of PD and other neurodegenerative diseases was obtained by in-person structured interview. We used the reconstructed cohort approach which provides a better estimate of the risk. The cumulative incidence of PD was significantly higher among relatives of PD patients compared to relatives of controls (2.0 versus 0.7%; RR=3.4, 95% CI 1.9–5.9; $p=0.0001$). The degree of familial aggregation was higher among first degree relatives of Hispanic PD cases compared to Hispanic controls (3.7% versus 0.4%; RR=8.5, 95% CI 1.0–68.9) than it was among non-Hispanic Caucasian cases and controls (2.0% versus 0.8%; RR=2.7, 95% CI 1.5–5.1) ($p=0.02$). The familial aggregation of PD was stronger among the siblings of PD

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Author Roles

Michael Shino carried out the statistical analyses, wrote the initial manuscript and participated in the critical review of the subsequent manuscript drafts. Valerie McGuire participated in execution of the research project and the design of the statistical analyses and wrote the subsequent manuscript drafts. Stephen K. Van Den Eeden participated in the conception, organization, and execution of the research project and critical review of the manuscript drafts. Caroline M. Tanner participated in the conception, organization, and execution of the research project and critical review of the manuscript drafts. Rita Popat participated in the execution of the research project and the critical review of the manuscript drafts. Allan Bernstein participated in the execution of the research project and the critical review of the manuscript drafts. Ms. Leimpeter participated in the execution of the research project and the critical review of the manuscript drafts. Lorene M. Nelson was the principal investigator, leading the conception, organization, and execution of the research project, the design of the statistical analysis, and the critical review of the manuscript drafts.

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cases (RR=5.4, 95% CI 1.8–16.0) than among parents (RR=2.7, 95% CI 1.3–5.2). The incidence and familial aggregation of PD is highest among Hispanics, warranting further studies of genetic and environmental risk factors in the Hispanic population.

Keywords

Parkinson's disease; risk factors; family history; case-control; epidemiology

Evidence suggests that genetic susceptibility and environmental factors play a role in the etiology of Parkinson's disease (PD).¹ Several case-control studies have reported an increased risk for PD among first-degree relatives of PD cases compared to PD among relatives of control subjects.^{2–24} Twin studies show no evidence for a genetic component among patients with typical older-onset disease,^{25–26} although Tanner et al.²⁶ reported a higher concordance rate among monozygotic twins diagnosed with PD before age 50 years. Mutations thought to result in monogenic forms of parkinsonism have typically been associated with young onset PD and account for a small proportion of all PD.²⁷

Most studies have examined the prevalence of family history of PD among cases and controls, a method that does not consider the number of affected relatives, family size, or person-years of follow-up. We assessed familial aggregation of PD in a community-based case-control study in a health maintenance organization (HMO) in Northern California. We collected detailed information on family history for PD and other neurodegenerative diseases and estimated the cumulative incidence of PD among first-degree relatives of cases and controls using the reconstructive cohort analysis method.

METHODS

Study population

The study was conducted within the Kaiser Permanente Medical Care Program (KPMCP) of Northern California, a large prepaid HMO. KPMCP provides comprehensive medical services to approximately 3 million members in the greater San Francisco Bay and Sacramento areas at the time of the study. The demographic characteristics of KPMCP members are closely representative of the underlying population with respect to sex, age, and race/ethnicity; however, members have a slightly higher education and income level.²⁸ A detailed description of the study design and methods for the incidence study is provided in a prior publication.²⁹ The Human Subject Committees at the Kaiser Foundation Research Institute and Stanford University approved the study.

Case ascertainment and control selection

We identified all newly diagnosed cases of PD 20 years or older in a two-year period from January 1 1994 through December 31 1995. We utilized several case-finding methods, including physician referrals, automated pharmacy records for PD-related medications, and computerized inpatient and outpatient records. A movement disorders specialist (CMT) reviewed each subject's medical records to apply the case definition slightly modified from published criteria.^{30,31} Patients were classified as having PD if they met the following criteria: (1) presence of at least two of the following signs: bradykinesia, cogwheel rigidity, resting tremor and postural reflex impairment, one of which must be resting tremor or bradykinesia; (2) no suggestion of another parkinsonian syndrome; (3) no atypical features; and (4) two of the following features: asymmetric onset, symptomatic improvement after treatment with L-dopa, or a progressive disease course. Medical records were reviewed for a two-year period after the diagnosis and we excluded 13 cases that developed clinical

features atypical of PD. In total, 573 PD cases met the case definition criteria and 496 (87%) agreed to participate in the study. Proxy interviews were required if the PD case had died between the time of diagnosis and recruitment (n=24; 4.8%) or cognitive impairment was identified either by the clinician or family members or as a result of a score of 23 or lower on the Mini Status Mental (MMSE) Exam (n=72; 14%).³²

Potential control subjects were randomly selected from KPMCP membership rolls and frequency matched to cases according to sex, age (by year of birth), and respondent type (self or proxy). Of the 720 eligible control subjects, 541 (75%) agreed to participate. Proxy respondents were sought for 51 controls (10.2%) who matched PD cases needing proxy respondents and for 41 control subjects (7.6%) cognitively impaired on the basis of the MMSE exam at the time of recruitment.

Data collection methods and exposure assessment

Data were collected through in-person structured interviews. All first-degree relatives were enumerated. For each relative, subjects were asked about the presence of the following physician-diagnosed conditions: PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Down's syndrome. In addition, subjects were asked if the relative ever had a tremor disorder or ever had trembling, shaking, or tremors every day. Age at diagnosis was obtained for each reported condition. The subjects were asked the current age of all living first-degree relatives (parents, siblings, and children) and the age of death for those who were deceased. Due to limited study resources, we were unable to interview relatives or obtain medical records of relatives to verify the diagnosis of PD or any of the other conditions. A positive family history was defined as one or more first-degree family members with a diagnosis of PD, ALS, AD, or tremor disorder. For each control of a given sex and birth year, a reference date was randomly assigned based on the case distribution for date of diagnosis within that group. Race/ethnicity was self-reported and classified as: non-Hispanic Caucasian, Hispanic Caucasian, Asian, and African American.

Statistical analysis

Statistical analyses were performed using SAS software. 33 Odds ratios (OR) and their 95% confidence intervals (CI) were calculated using stratified data analysis and unconditional logistic regression.³⁴ Statistical tests of the regression estimates were based on the chi-squared approximation for the likelihood ratio statistic³⁵ and 95% CI on Wald's test. All models were adjusted for matching variables sex and age, and for race/ethnicity, and smoking (pack-years). We were unable to estimate the risk of family history for PD in the proxy respondents separately because the control proxy respondents did not report any first-degree relatives with PD for their corresponding control. Thus, all analyses excluded the data from proxy respondents, reducing the number of subjects to 400 cases and 448 controls.

To assess familial aggregation of PD, we estimated the cumulative incidence of PD among first-degree relatives using the reconstructed cohort approach.³⁶ We restricted our analysis to parents and siblings because none of the children had developed PD. The relative risk (RR) for PD among parents and siblings of PD cases compared to controls was estimated using Cox proportional hazard models,³⁷ allowing us to control for age and number of relatives. Double censoring techniques were used for missing information. If the relative was known to have PD but age at diagnosis was unknown or missing (7 relatives of cases (15%), 2 relatives of controls (13%)), left censoring was applied, and the relative's current age or age at death was used. If the relative did not develop PD and either current age or age at death was unknown (76 relatives of cases (4%), 127 relatives of controls (5%)), the average current age for all other relatives of that relationship type was imputed. The model was adjusted for race/ethnicity of the case (non-Hispanic Caucasian /Other), sex of the

relative, and the relationship type (parent/sibling). The race/ethnicity of the subject was used as a proxy for the ethnicity of the relative. We also stratified on sex, race/ethnicity, and relationship type. We utilized the same methodology to estimate the RR for the other diagnoses among first-degree relatives of PD cases and controls.

RESULTS

Case and control subjects were closely matched on age and sex. The average age at reference date was 70 years in both groups, and 60% of the subjects were male. The cases and controls were similar with respect to race/ethnicity (table 1) and education, but differed with respect to smoking status. Cases were less likely to have ever smoked (51.6% of cases and 59.7% of controls, $p<0.02$) or to be current smokers (2.3% of cases and 13.8% of controls, $p<0.001$). PD cases reported 2,014 first-degree relatives and the control subjects, 2,165 first-degree relatives. The sex and age distributions of the relatives were similar for cases and controls. Sibship size and mean number of person-years were similar for the two groups (table 1).

In keeping with other studies, we compared the prevalence of a positive family history of PD among cases and controls. Parkinson's disease cases were more likely to have one or more first-degree relatives diagnosed with PD ($n=43$, 11%) than were control subjects ($n=16$, 4%), and the associated OR was 3.1 (95% CI 1.7–5.7). Only 4 cases (and no controls) reported having two affected first-degree family members with PD.

Table 2 contrasts the characteristics of PD probands who had one or more affected first-degree family member with probands who had no affected relatives. These two groups were similar in age, but significantly different with respect to sex, sib-ship size, and mean number of person years. Cases with familial PD cases were more likely to be female (56%) than were non-familial cases (38%; (table 2)). Familial PD cases had higher average sib-ship size and were more likely to be Hispanic Caucasian.

The cumulative incidence of PD was significantly higher in relatives of PD cases compared to relatives of controls (RR=3.4; 95% CI 1.9–5.9) (table 3, figure 1a). The cumulative incidence of PD was five-fold higher among relatives of female probands than relatives of female controls, whereas the cumulative incidence of PD was increased only two-fold among relatives of male PD probands (test for interaction=0.15, figure 1b). The degree of familial aggregation was higher among first degree relatives of Hispanic PD cases compared to Hispanic controls (RR=8.5, 95% CI 1.0–68.9) than it was among non-Hispanic Caucasian cases and controls (RR=2.7, 95% CI 1.5–5.1) ($p=0.02$). Stratifying on age at diagnosis of PD in cases, the RR was slightly, but not significantly ($p=0.48$), higher among relatives of cases who were less than 60 years at diagnosis (RR=4.0) than relatives of probands who were 60 years or older at diagnosis (RR=3.0–3.2).

The familial aggregation of PD was somewhat stronger among the siblings of PD probands (RR=5.4) than among parents (RR=2.7), ($p=0.25$) (table 3, figure 1c). The risks were similar for fathers compared to mothers, as well as for brothers compared to sisters.

Among the family members of PD probands and controls, the cumulative incidences of AD and ALS were similar among relatives of PD cases and controls. Relatives of cases had a nearly two-fold increase in risk of tremor disorder with daily tremor than did relatives of controls (RR=1.9, 95% CI 0.9–4.3).

DISCUSSION

In our study, first-degree relatives of cases had a greater than three-fold increased risk of PD compared to relatives of controls after adjusting for sex, race/ethnicity of proband, and relationship type (parent or sibling). Our findings are best compared with published community-based studies that used the reconstructed cohort method,^{8,18,22,23} and with a recent meta analysis of PD familial aggregation studies.³⁸ Thacker and Ascherio³⁸ categorized studies with respect to four methodological criteria: (1) enumeration of relatives for PD classification, (2) confirmation of PD in relatives by direct examination, (3) population-based study sample with controls randomly selected from the same population, and (4) use of the reconstructed cohort statistical analysis strategy. Our study fulfilled criteria (1), (3), and (4). We enumerated and classified each first-degree relative (criteria 1), enabling application of the reconstructed cohort analysis method (criteria 4). We identified cases from a large well-defined HMO population, representative of the underlying geographic area (criteria 3) and the degree of ascertainment was high, given the comparability of our PD incidence rates to those of the Olmstead County population. In addition, the case group was restricted to newly diagnosed cases of PD, to avoid differentiating between factors associated with better survival and those that affect the initial development of PD. The primary limitation of our study is self-report of family history data. We did not interview affected relatives nor obtain medical records to verify the relative's diagnosis of PD or other neurological disorders.

Our finding of a relative risk of 3.4 (95% CI 1.9–5.9) among first-degree relatives of PD probands is identical to the meta-analysis summary RR reported by for studies that fulfilled three of the four most rigorous methodological criteria (RR=3.4, 95% CI 2.7–4.5).³⁸ This estimate is slightly higher than the meta-analytic summary for studies that employed all four criteria (RR=2.9, 95% CI 2.2–3.8),³⁸ possibly due to case probands over-reporting and control subjects under-reporting PD among their first-degree relatives.³⁹

Our findings of a somewhat stronger familial aggregation among sibling of PD probands than among parents, while not statistically significant, are consistent with the meta-regression model results (summary RR=4.4 (95% CI 3.1–6.1) among siblings; summary RR=2.7 (95% CI 2.0–3.7) among parents).³⁸ The differences in risk of PD between siblings and parents of PD probands may be due to several factors: 1) siblings are contemporaries of probands and therefore may be more likely to be diagnosed with PD because of improved health care in recent years; 2) probands may be more aware of a living siblings' PD diagnosis than that of their deceased parents; and 3) siblings have a greater degree of shared environment than do parents. The multiethnic composition of our study population enabled us to examine familial aggregation separately for three racial/ethnic groups: Hispanic Caucasians, non-Hispanic Caucasians and Asian Americans. We observed a greater than eightfold increase in risk of PD among first-degree relatives of Hispanic PD cases compared to first-degree relatives of Hispanic controls (RR=8.5). In contrast, the relative risk of PD among the first-degree family members was much lower among non-Hispanic Caucasians (RR=2.7), and among Asians (RR=2.1). In the PD incidence study we conducted in the KPMCP population, Hispanics had the highest incidence rate for PD among the four racial ethnic groups (16.6/10⁵, 95% CI 12.0–21.3), higher than non-Hispanic Caucasians (13.6, 95% CI 11.5–15.7), Asian-Americans (11.3, 95% CI: 7.2–15.3), and African-Americans (11.3, 95% CI 7.2–15.3).²⁸ The average age at PD diagnosis was lowest for Hispanics ($\bar{X}$ =63.1, $\pm$ 10.7 yrs) than it was for the non Hispanic Caucasians ($\bar{X}$ = 69.4, $\pm$ 9.2 yrs) ($p<0.0007$). Hispanics appear to be at higher risk for the occurrence of PD, possibly due to environmental or genetic factors not yet identified. Almost all previous studies of familial aggregation of PD have been conducted in Caucasian or northern European populations, with two exceptions, a study in the USA that did not report risk in the Hispanic Caucasian

population²³ and one in China.⁴⁰ Our results require confirmation in studies with larger numbers of Hispanic subjects for a more precise risk estimate.

Because Parkinson's disease, AD, and ALS share some clinical and pathological characteristics, a possible shared environmental and/or genetic susceptibility to these disorders has been proposed.⁴¹ In our study, we found no significant difference in the cumulative incidence of AD between relatives of PD cases and relatives of controls. Three other studies noted a similar result for PD cases without dementia.^{42–44} We also found no significant increase in risk of ALS in relatives of cases compared to relatives of controls.

We observed a nearly two-fold increased risk for tremor disorder with daily tremors among relatives of cases compared to relatives of controls. Louis et al.⁴⁵ reported a two-fold increased risk for action tremor endorsed among first-degree relatives of tremor-dominant PD cases compared to first-degree relatives of controls (RR=2.1, 95% CI 1.5–3.0). The study relied on self-reported information from cases and controls, so family bias may have affected reporting, in that awareness of tremor in relatives was more likely among PD patients with tremor and less likely among controls. However, when Louis et al.⁴⁵ assessed potential bias and validated reported tremor in a subgroup of relatives, bias was not apparent in their population. The investigators speculated that this tremor represented mild parkinsonian tremor, or possibly essential tremor. The association between essential tremor and PD has been suggested since the 1980's but has not been observed in all studies.^{46–49} Future family studies, including careful clinical characterization of tremor in relatives, will help to determine whether PD and other tremor disorders are linked by the same genetic markers or pathogenic mechanisms.

Although this study confirms the aggregation of PD within families, it does not explore whether genetic or environmental factors are involved in this clustering. The possibility of shared environmental exposures among family members or the combination of genetic and environmental factors cannot be ruled out. Studies in Hispanic populations which have the highest incidence and the strongest familial aggregation of PD are a priority. Candidate gene studies may shed some light on the extent to which susceptibility genes are involved in the clustering of PD. The results of this study warrant further research in order to gain an understanding of the role that genetic and environmental factors play in the familial aggregation of Parkinson's disease.

ABBREVIATIONS

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
CI	confidence intervals
KPMCP	Kaiser Permanente Medical Care Program
OR	odds ratio
PD	Parkinson's disease
RR	relative risk

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Figure 1a

Figure 1b

Figure 1c

Figure 1.

Cumulative incidence of Parkinson's disease in first-degree relatives of PD cases and controls, (a) all relatives, (b) by sex of proband, and (c) by relationship to proband, Kaiser Permanente Medical Care Program (KPMPC) of Northern California, 1994–1995. Person-years is the sum of the time that each individual was under observation and remained free of disease.

TABLE 1

Characteristics of PD cases and controls, Kaiser Permanente Medical Care Program (KPMPC) of Northern California, 1994–1995.

Characteristic	PD cases (n=400)	Controls (n=448)	<i>p</i> -value*
Age at time of the study, mean (range)	70.1 (33–95)	70.4 (33–95)	0.61
Age at diagnosis of PD, mean (range)	68.6 (31–93)		
Female, n (%)	160 (40%)	178 (40%)	0.94
Race/ethnicity,			
White non-Hispanic	334 (83%)	366 (82%)	
White Hispanic	12 (3%)	28 (6%)	
African American	29 (7%)	33 (7%)	0.12
Asian	22 (6%)	17 (4%)	
Other	3 (1%)	1 (1%)	
Sibship size, mean (range)	3.4 (0–14)	3.2 (0–15)	0.44
Sibship size, mean number of person-years(range)	195 (0–893)	185 (0–877)	0.36

* two sided *p*-value

TABLE 2

Characteristics of familial and non-familial PD cases, Kaiser Permanente Medical Care Program (KPMPC) of Northern California, 1994–1995.

Characteristic	PD cases with affected relatives (n=43)	PD cases without affected relatives (n=357)	<i>p</i> -value*
Age at time of the study, mean (range)	70.5 (52–91)	70.0 (33–95)	0.76
Age at diagnosis of PD, mean (range)	69.1 (51–90)	68.5 (31–93)	0.71
Female, n (%)	24 (56%)	136 (38%)	0.03
Race/ethnicity,			
White non-Hispanic	32 (74%)	302 (85%)	0.17
White Hispanic	6 (14%)	23 (6%)	
Asian	4 (9%)	18 (5%)	
Other	1 (2%)	14 (4%)	
Sibship size, mean (range)	4.5 (0–14)	3.2 (0–12)	0.01
Sibship size, mean number of person-years (range)	256 (0–893)	188 (0–720)	0.01

* two sided *p*-value

TABLE 3

Relative risk of neurological disorders in first-degree relatives of PD cases and controls, Kaiser Permanente Medical Care Program (KPMPC) of Northern California, 1994–1995

Characteristic	Affected relatives of cases (%)	Total number of relatives of cases	Affected relatives of controls (%)	Total number of relatives of controls	RR (95% CI) *	p-value *
PD diagnosis	47 (2.0)	2014	16 (0.7)	2165	3.4 (1.9–5.9)	< 0.01
Sex						
Female	28 (3.3)	856	6 (0.7)	893	5.3 (2.2–12.9)	< 0.01
Male	19 (1.6)	1158	10 (0.8)	1272	2.1 (1.0–4.6)	0.05
Race/ethnicity						
White, non-Hispanic	34 (2.0)	1574	14 (0.8)	1683	2.7 (1.5–5.1)	< 0.01
White, Hispanic	8 (3.7)	199	1 (0.4)	209	8.5 (1.0–68.9)	0.04
Asian	4 (2.5)	54	1 (0.9)	97	2.1 (0.2–20.1)	0.50
Other	1					
Age at diagnosis (yrs) †						
< 60	7 (2.1)	321	4 (1.0)	385	4.0 (1.6–10.0)	< 0.01
60–74	23 (2.0)	1076	8 (0.7)	1054	3.0 (1.6–5.8)	< 0.01
> 75	17 (2.5)	617	4 (0.5)	726	3.2 (1.6–6.5)	< 0.01
Relationship						
Parent	28 (3.5)	769	12 (1.3)	861	2.7 (1.3–5.2)	< 0.01
Father	14 (3.7)	376	5 (1.2)	421	3.2 (1.2–8.9)	0.03
Mother	14 (3.6)	393	7 (1.6)	440	2.3 (0.9–5.7)	0.07
Relationship						
Sibling	19 (1.4)	1245	4 (0.3)	1304	5.4 (1.8–16.0)	< 0.01
Brother	11 (1.8)	613	2 (0.3)	646	6.2 (1.4–28.1)	0.02
Sister	8 (1.3)	632	2 (0.3)	658	4.9 (1.0–23.1)	0.05
Other conditions						
Alzheimer's disease	31 (1.4)	2016	34 (1.5)	2159	1.1 (0.7–1.7)	0.80
ALS	6 (0.3)	2024	3 (0.1)	2171	2.2 (0.6–9.0)	0.25
Tremor diagnosis ‡	17 (0.9)	1962	10 (0.5)	2148	1.9 (0.9–4.3)	0.09

* RR, relative risk; CI, confidence interval; two-sided p-value. RR adjusted for sex, white non-Hispanic (case) and relationship. Double censoring techniques used for missing information.

[†] Age at diagnosis for PD case; referent group for each age strata is all relative controls.

[‡] Relatives with a tremor diagnosis and daily tremors excluding those with PD.