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Familial Associations of Alzheimer Disease and Essential Tremor with Parkinson Disease

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Abstract

Background—We constructed a cohort of first degree relatives of participants in a population-based case-control study of Parkinson disease (PD) and compared the occurrence of Alzheimer disease (AD) and essential tremor (ET) in relatives of PD cases and controls.

Methods—We relied on proband interviews to assess family history in 372 probands with incident PD confirmed by a movement disorder specialist and 404 controls from three rural California counties.

Results—Overall, for the 2980 first degree relatives of PD cases the risk of AD was not increased compared with the 2981 relatives of controls. But relatives of younger onset PD cases (<=60 years of age) were three times more likely to have received an AD diagnosis (HR: 2.86; 95%CI: 1.44, 5.71). Our data also suggest that some relatives of PD probands might be at a slightly increased risk of receiving an ET diagnosis, especially relatives of tremor dominant cases (HR: 1.69; 95%CI 0.99, 2.88), younger onset cases (HR: 2.03; 95%CI 0.93, 4.44), and male relatives (HR: 2.31; 95%CI 1.13, 4.73). In addition, fathers of cases were almost 15 years younger than fathers of controls when diagnosed with ET. Results were stable in sensitivity analyses.

Conclusion—Our study suggests a familial susceptibility to AD among first degree relatives of younger onset PD cases.

Keywords

Epidemiology; Parkinson’s disease; Tremor; Alzheimer’s disease; Familial Aggregation

Parkinson’s disease (PD) and Alzheimer disease (AD), the two most common neurodegenerative disorders, and essential tremor (ET), a common movement disorder, have been found to co-occur in some families suggesting that common pathophysiological mechanisms may underly these disorders. The pathologies of PD and AD are characterized by accumulations of abnormally processed proteins, α-synuclein in Lewy bodies in PD, and tau and amyloid in AD[1]. In addition, Lewy bodies have recently been found in the brains of patients with ET[2] and abnormal F-dopa PET scans support nigrostriatal involvement in some ET patients.[3] Only two population-based studies to date have examined familial aggregation of dementia and tremor among first degree relatives of PD cases and controls. Both investigations, one based in Northern Manhattan, NY and the other in Olmsted County, MN found elevated tremor risks in first degree relatives of PD cases, especially tremor-dominant PD cases.[4,5] Only the MN group reported an elevated risk for developing dementia or cognitive impairment among relatives of PD cases.[6,7]

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We conducted a population-based case-control study enrolling 372 incident PD cases and 404 central California population controls and assessed the influence of environmental and genetic factors on PD development. Here we investigate familial aggregations of AD and ET with PD using family history interviews conducted with PD cases and controls. Our study allows us to re-assess the two previous reports within a population-based framework.

Methods

All study procedures were approved by the University of California, Los Angeles, human subjects committee and all subjects signed an informed consent form.

Subject Recruitment

In a population-based manner we recruited study subjects in Fresno, Tulare, and Kern Counties, California. Case definition and recruitment criteria have been described elsewhere. [8,9] Briefly, through neurology offices, clinics, and public service announcements, new-onset PD cases (diagnosed after January 1, 1998) and controls residing in these counties, were recruited between 2001 and 2007. We established a diagnosis of probable or possible idiopathic PD in 385 of 473 cases examined (those excluded suffered from Parkinsonism); 372 provided the information needed for analyses.

A total of 1297 potential controls recruited from Medicare lists and randomly selected living units were contacted and screened for eligibility by mail and phone. Of those, 500 were ineligible (too young N=430, terminally ill N=61, not primarily residing in the counties N=9). Out of 797 eligible population controls, 404 (50.7%) were enrolled and provided the information for this analysis. The others declined participation, were too ill, or moved out of the area.

Outcome and exposure assessment

UCLA movement disorder specialists examined all potential PD cases and administered the motor portion of the United Parkinson's Disease Rating Scale. Most examinations were performed when cases had not taken PD medications for at least 12 hours. Case and control probands provided their family history for PD, AD and ET in a standardized interview and participated in the Mini Mental State Exam (MMSE). Demographic and risk factor data were also collected by trained interviewers.

Probands reported diagnoses of AD and ET in first degree relatives ("Did or do any of your relatives *(list of first degree relatives)* have Parkinson's disease, Essential or Familial tremor (uncontrollable shaking of the hands or arms), Alzheimer's disease, or other dementia" followed by "Which relative?" and "Age at diagnosis"); if the relative was deceased we recorded age at death; we also recorded ages for living parents.

Statistical methods

We hypothesize that family members share a vulnerability to neurodegenerative diseases due to genetic or environmental factors; thus, we expect higher rates of AD and ET in first degree relatives of PD patients than among population controls. Employing Cox proportional hazard models, we calculated hazard ratios (HR) for developing AD or ET among first degree relatives. We censored relatives either at their ages of onset of AD or ET, their current age (at the time of the probands' interview), or their age of death whichever came first. Relatives with a PD diagnosis remained at risk for AD or ET until the time of the proband interview or their death, if applicable. Since we did not collect the ages of living siblings (N=1661, 71.2%) or offspring (N=1959, 93.8%), for censoring purposes the ages of living siblings were imputed with the age of the proband and the ages of living offspring

were imputed with the age of the proband minus 24 years for female probands (average age of women giving birth in 1970[10])and 27 years for male probands (on average men were 3 years older than their first wives in the 1960s[11]). We imputed missing ages of death for siblings (N=148, 6.3%) and offspring (N=28, 1.3%) using Proc MI in SAS 9.1 (SAS Institute Inc., Cary, NC, USA) based on the information available for other sibling or offspring ages at death, their sex, and the proband's case or control status, age, race, education and sibship size. Missing age at onset for siblings (AD: N=1, ET: N=2) was imputed with the proband age and for parents (AD: N=1, ET: N=5) either with the parents' current age or age of death (carry-forward imputation). Data for offspring age at diagnosis were complete.

All Cox models were adjusted for the sex of the relative, and the proband's education (<12, 12, >12 years) and minority status (yes/no). We also conducted stratified analyses by type of PD (akinetic-rigid, tremor-dominant and mixed-type) and age of PD diagnosis (<=60 years of age vs. >60). We choose age 60 as the *a priori* cutoff for age-at-diagnosis since we did not enroll enough younger PD probands for the more typical cutoff age of 50. The definition of the PD subtypes are described elsewhere.[8]

We used T-tests, crude and stratified by sex of the parent, to assess differences for age at diagnosis for both AD and ET comparing the parents of PD and control probands.

Results

A total of 2980 relatives of 372 PD cases were compared with 2981 relatives of 404 population controls (Table 1). Case probands reported more PD occurrence among first degree relatives than controls. Cases were slightly older, more often male and of white race while controls tended to be more educated. Non-white families were slightly larger in size (over 50% of non-white probands had more than 3 siblings vs. 25% of white probands) while higher educated probands reported smaller families (27% had more than 3 siblings vs. 59% of probands with less than 12 years of school). Over half of the probands with PD presented as akinetic-rigid, a third as tremor-dominant, and the rest with a mixed type. A fifth (22%) of our patients were first diagnosed with PD at 60 years of age or younger.

First degree relatives of PD cases were not at an increased risk of AD in our sample nor did stratification by proband's PD type suggest any differential in risk (Table 2). However, for relatives of younger onset PD cases we estimated an almost three-fold increase in risk for an AD diagnosis (HR: 2.86; 95%CI: 1.44, 5.71). Our results also suggest that relatives of PD probands are at a slightly increased risk of receiving an ET diagnosis, especially relatives of tremor-dominant cases, but we lacked statistical power to estimate these moderately size associations more precisely. Importantly, relatives of younger onset PD cases were twice as likely to have received an ET diagnosis (HR: 2.03; 95%CI: 0.93, 4.44) as were male relatives (HR: 2.31; 95%CI: 1.13, 4.73).

None of these effect estimates changed appreciably when subjected to sensitivity analyses, such as a) excluding relatives with a PD diagnosis, b) excluding relatives of probands with low MMSE scores (< 23 for the in-person or < 20 for the telephone MMSE) indicating mild cognitive impairment, c) combining reports of "other dementia" in first degree relatives with reports of AD (Table 2a) and d) restricting to probands of white race only (data not shown). When conducting analyses for proband parents only, parents of younger onset cases were still at an increased risk of AD (HR: 2.42; 95%CI: 1.19, 4.91). However, the associations with ET were weaker in the parent-only cohort than for all first degree relatives (parents of all cases HR: 1.08; 95%CI: 0.60, 1.95 and parents of younger cases HR: 1.36; 95%CI: 0.55, 3.36). When we excluded probands with a diagnosis of "possible" PD the increased risk of

AD remained stable in relatives of younger cases (HR: 2.67; 95%CI: 1.30, 5.48), while the risk of ET decreased (HR for relatives of all cases was 1.21 and for younger onset cases 1.56, both 95% CIs included the null value).

Examining reported age at diagnosis, parents of PD probands were on average almost 9 years younger, and fathers more than 14 years younger, than their control counterparts when diagnosed with ET (Table 3).

Discussion

Familial Aggregation of AD

In this population-based study in the Californian central valley, risk of AD was found to be increased in families of younger onset PD cases, but not overall. Ours is the third large population-based study in which familial aggregation of AD has been explored in a cohort of first degree relatives of PD cases and controls. In Manhattan, researchers investigated AD in families of PD cases recruited from two clinics and in controls living in the same neighborhood as cases, by administering detailed family history interviews to probands, their relatives and other informants, whenever possible. They did not find an increase in AD risk among first degree family members of PD patients,[6] however, when stratifying PD cases according to a dual diagnosis of dementia and PD, a three-fold increased risk of AD in siblings of PD patients with dementia emerged.[12] By design, we only recruited and examined new-onset cases of PD without dementia, and thus were unable to explore the familial aggregation of AD by probands' dementia status. A second population-based study recently reported an increased risk of dementia in first degree relatives of patients with younger onset PD (<66 years old) in the Mayo Clinic population of Olmsted County.[7] These researchers interviewed and cognitively tested many first degree relatives of their probands and reviewed medical records for dementia or cognitive impairment in some relatives. Although we relied solely on proband reports of AD and other dementias in family members, our results of an increased risk of AD in first degree relatives of younger onset PD confirmed this report.

Patients with AD are more likely than non-diseased elderly to exhibit extrapyramidal signs[13–15] and dementia often occurs in the course of PD.[16,17] This clinical overlap may point to pathological similarities in patients from families with co-occurrence of these diseases, particularly the accumulation of abnormally processed proteins. In fact, examinations of brains of AD patients revealed the existence of Lewy bodies in cases with clinical manifestations of parkinsonian symptoms.[18,19] In cell and animal models, tau and α-synuclein synergistically promote each others fibrillization and beta-Amyloid peptides promote aggregation of alpha-synuclein; furthermore alpha-synuclein and tau filamentous amyloid inclusions have been found in humans providing further links between PD and AD pathophysiology.[20–22]

Familial Aggregation of ET

Risk of ET in our study was moderately increased in families of PD cases overall, as well as in families of tremor-dominant PD, younger onset PD, and male relatives of PD probands, however the weaker associations were estimated imprecisely.

Two previous studies[4,5] employed detailed interviews concerning ET in relatives and in Olmsted county researchers additionally conducted some in-person examinations or medical record reviews for relatives. Compared with earlier reports, these studies used greatly improved assessments.[23] One study found a higher incidence of action tremor in family members of patients with tremor-predominant PD,[4] supporting our findings for this PD subtype. The other study[5] reported a twofold increase in risk of ET in first degree relatives

of younger PD patients (onset <66 years of age) and an elevated risk of ET in relatives of patients with tremor-dominant or mixed forms of PD, an association that was even stronger in sibling and offspring-only analyses. Confirming these previous observations, the hazard ratio for ET among siblings and offspring (excluding parents) of our cases was 2.48 (95% CI: 1.09, 5.61) based on 22 affected relatives of PD cases and only 8 affected relatives of controls.

Additionally, average age at diagnosis of ET in our study was 14 years lower for fathers of cases compared with controls. Such an age difference was not found for AD, PD or other dementia suggesting that the age difference for ET onset is a unique phenomenon. Corroborating the Olmsted study results further, we observed an increased risk of ET primarily in male first degree relatives, which, in combination with the younger age at onset of ET in fathers of PD probands, may indicate that different factors contribute to familial associations of ET and PD in men. To our knowledge, ours is the first study to publish an association between PD and younger age of onset for ET in male first degree relatives.

The unifying characteristic of ET is a kinetic tremor usually diagnosed when no known cause or associated neurological signs are present; but recently the concept emerged that ET might be a family of diseases heterogeneous with regard to etiological, clinical and pathological features.[24] For example, a recent case study of a multigenerational family complex reported an admixture of ET and PD lending support to possible familiar overlap of PD and ET pathologies.[25] Another study suggested that patients with PD were more likely to have a prior diagnosis of ET than patients with Parkinson-plus syndromes.[26] Furthermore, a 18F-dopa PET study reported that 17% of patients with a postural tremor had abnormal tracer uptake suggesting an alteration of the nigrostriatal dopaminergic system.[3] In addition, recent work by Louis et al., revealed the existence of Lewy body pathology in 24% of subjects diagnosed with ET clinically.[27] It may not be surprising that relatives of patients with tremor-dominant PD were more often diagnosed with ET as postural tremor might be the first manifestation of PD.[25,26]

Some familial forms of PD attributed to gene mutations or genetic susceptibility factors are characterized by early onset of disease. Genes implicated thus far include alpha-synuclein, parkin, PINK1, DJ-1 and glucocerebrosidase; additional neurologic symptoms or diagnoses (including dementia) have been described in association with these genes.[28] This supports the increased risks for AD and ET that were found in our younger onset PD cases. Also, a recent population based study found that ET cases with tremor onset after age 65 years were more likely to develop incident dementia than were controls, again linking both diseases.[29,30] The coexistence of both AD and ET with PD in families of our younger onset case probands is in agreement with the clinical overlap that has been reported for these disorders and lends further support to the idea of exploring possible common pathophysiological mechanisms for these processes.

Strengths and Weaknesses

An advantage of our study is the recruitment of incident PD cases and population controls. Unfortunately, our population-based design did not permit the confirmation of ET and AD in family members by physical examination, interview, or medical record review. Most of the relatives old enough to have developed one of these neurodegenerative diseases were parents of elderly probands, but 85% were deceased at the time of the proband's interview. We conducted sensitivity analyses excluding all relatives of probands with a lower MMSE to limit recall bias due to a proband's failing memory and results did not change, possibly because subjects received help from family members when reporting family history. We also presented analyses for parents only, excluding siblings and offspring with imputed censoring ages. Again, this did not change our conclusions.

Recall bias is a possible explanation for the apparent familial aggregation of AD and ET in parents of younger onset probands since PD cases may be more aware of PD in parents or may even over-report PD in unaffected parents.[31] Here PD cases would have to be more aware of, or over-report, AD or ET in family members for a positive bias to result. Since we did not observe a familial aggregation of AD in all family members, recall bias seems less compelling an explanation as one would expect such a bias to operate for both ET and AD independent of sex of the relative, PD type, and age at onset of PD. Recall bias is also less likely to affect information related to age at onset of ET in parents as cases would have no apparent reason to report younger onset of ET in fathers, even if they over-reported the disease.

The younger age of onset for ET in fathers of PD cases seems intriguing and should be explored further. Overall, our study lends some support to a familial susceptibility to AD and ET among first degree family members of mostly younger onset (<=60 years of age) Parkinson's disease cases.

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References

1. Yoshimoto M, Iwai A, Kang D, Otero DA, Xia Y, Saitoh T. NACP, the precursor protein of the non-amyloid beta/A4 protein (A beta) component of Alzheimer disease amyloid, binds A beta and stimulates A beta aggregation. Proc Natl Acad Sci U S A. 1995; 92(20):9141–5. [PubMed: 7568089]
2. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007; 130(12):3297–307. [PubMed: 18025031]
3. Brooks DJ, Playford ED, Ibanez V, Sawle GV, Thompson PD, Findley LJ, et al. Isolated tremor and disruption of the nigrostriatal dopaminergic system: an 18F-dopa PET study. Neurology. 1992; 42(8):1554–60. [PubMed: 1641153]
4. Louis ED, Levy G, Mejia-Santana H, Cote L, Andrews H, Harris J, et al. Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD. Neurology. 2003; 61(7):931–6. [PubMed: 14557562]
5. Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, et al. Increased risk of essential tremor in first-degree relatives of patients with Parkinson's disease. Mov Disord. 2007; 22(11):1607–14. [PubMed: 17546668]
6. Levy G, Louis ED, Mejia-Santana H, Cote L, Andrews H, Harris J, et al. Lack of familial aggregation of Parkinson disease and Alzheimer disease. Arch Neurol. 2004; 61(7):1033–9. [PubMed: 15262733]
7. Rocca WA, Bower JH, Ahlskog JE, Elbaz A, Grossardt BR, McDonnell SK, et al. Risk of cognitive impairment or dementia in relatives of patients with Parkinson disease. Arch Neurol. 2007; 64(10): 1458–64. [PubMed: 17923629]
8. Kang GA, Bronstein JM, Masterman DL, Redelings M, Crum JA, Ritz B. Clinical characteristics in early Parkinson's disease in a central California population-based study. Mov Disord. 2005; 20(9): 1133–42. [PubMed: 15954133]
9. Costello S, Cockburn M, Bronstein J, Zhang X, Ritz B. Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California. Am J Epidemiol. 2009; 169(8):919–26. [PubMed: 19270050]
10. Mathews, TJ.; Hamilton, BE. Reports NVS. Mean Age of Mother, 1970–2000. Hyattsville, Maryland: National Center for Health Statistics; 2002.

11. Clarke, SC. Report MVS. Advance Report of Final Marriage Statistics, 1989 and 1990. Hyattaville, Maryland: National Center for Health Statistics; 1995.
12. Marder K, Tang MX, Alfaro B, Mejia H, Cote L, Louis E, et al. Risk of Alzheimer's disease in relatives of Parkinson's disease patients with and without dementia. Neurology. 1999; 52(4):719–24. [PubMed: 10078716]
13. Chen JY, Stern Y, Sano M, Mayeux R. Cumulative risks of developing extrapyramidal signs, psychosis, or myoclonus in the course of Alzheimer's disease. Arch Neurol. 1991; 48(11):1141–3. [PubMed: 1953398]
14. Ellis RJ, Caligiuri M, Galasko D, Thal LJ. Extrapyramidal motor signs in clinically diagnosed Alzheimer disease. Alzheimer Dis Assoc Disord. 1996; 10(2):103–14. [PubMed: 8727172]
15. Mitchell SL. Extrapyramidal features in Alzheimer's disease. Age Ageing. 1999; 28(4):401–9. [PubMed: 10459796]
16. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003; 60(3):387–92. [PubMed: 12633150]
17. Levy G, Schupf N, Tang MX, Cote LJ, Louis ED, Mejia H, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol. 202;51(6):722–9.
18. Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, DeTeresa R, et al. The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology. 1990; 40(1):1–8. [PubMed: 2153271]
19. Heyman A, Fillenbaum GG, Gearing M, Mirra SS, Welsh-Bohmer KA, Peterson B, et al. Comparison of Lewy body variant of Alzheimer's disease with pure Alzheimer's disease: Consortium to Establish a Registry for Alzheimer's Disease, Part XIX. Neurology. 1999; 52(9): 1839–44. [PubMed: 10371532]
20. Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, et al. Initiation and synergistic fibrillization of tau and alpha-synuclein. Science. 2003; 300:636–40. [PubMed: 12714745]
21. Kotzbauer PT, Giasson BI, Kravitz AV, Golbe LI, Mark MH, Trojanowski JQ, et al. Fibrillization of alpha-synuclein and tau in familial Parkinson's disease caused by the A53T alpha-synuclein mutation. Exp Neurol. 2004; 187(2):279–88. [PubMed: 15144854]
22. Masliah E, Rockenstein E, Veinbergs I, Sagara Y, Mallory M, Hashimoto M, et al. Beta-amyloid peptides enhance alpha-synuclein accumulation and neuronal deficits in a transgenic mouse model linking Alzheimer's disease and Parkinson's disease. Proc Natl Acad Sci USA. 2001; 98(21): 12245–50. [PubMed: 11572944]
23. Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord. 2007; 13(2):67–76. [PubMed: 16887374]
24. Benito-León J, Louis ED. Essential tremor: emerging views of a common disorder. Nat Clin Pract Neurol. 2006; 2(12):666–78. [PubMed: 17117170]
25. Yahr MD, Orosz D, Purohit DP. Co-occurrence of essential tremor and Parkinson's disease: clinical study of a large kindred with autopsy findings. Parkinsonism Relat Disord. 2003; 9(4): 225–31. [PubMed: 12618058]
26. Louis ED, Frucht SJ. Prevalence of essential tremor in patients with Parkinson's disease vs. Parkinson-plus syndromes Mov Disord. 2007; 22(10):1402–7.
27. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007 Dec; 130(Pt 12): 3297–307. [PubMed: 18025031]
28. Lesage S, Brice A. Parkinson's disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet. 2009; 18(R1):R48–59. [PubMed: 19297401]
29. Benito-León J, Louis ED, Bermejo-Pareja F. Neurological Disorders in Central Spain Study Group. Elderly-onset essential tremor is associated with dementia. Neurology. 2006; 66(10):1500–5. [PubMed: 16717208]
30. Bermejo-Pareja F, Louis ED, Benito-León J. Neurological Disorders in Central Spain (NEDICES) Study Group. Risk of incident dementia in essential tremor: a population-based study. Mov Disord. 2007; 22(11):1573–80. [PubMed: 17516478]

31. Elbaz A, McDonnell SK, Maraganore DM, Strain KJ, Schaid DJ, Bower JH, et al. Validity of family history data on PD: evidence for a family information bias. Neurology. 2003; 61(1):11–7. [PubMed: 12847149]

Table 1

Demographic and Clinical Characteristics of the Probands with Parkinson Disease (PD) and Control Probands and their First Degree Relatives

	Probands with PD (n = 372)	Control Probands (n = 404)	Relatives of Probands with PD (n =2,980)	Relatives of Control Probands (n = 2,981)
Age, mean (SD)	68.0 (10.4)	65.9 (12.4)	58.4 (18.3)	55.9 (19.6)
Male	208 (55.9)	199 (49.3)	1548 (52.0)	1504 (50.5)
12 years or more of education	306 (82.3)	359 (88.9)	2249 (75.5)	2549 (85.5)
White race	303 (81.5)	316 (78.2)	2265 (76.0)	2184 (73.3)
Younger PD Onset(<=60)**	81 (21.8)	120 (29.7)	553 (18.6)	838 (28.1)
Age, mean (SD)	52.3 (7.0)	50.2 (6.8)	47.5 (17.8)	42.8 (18.0)
Male	48 (59.3)	42 (35.0)	294 (53.2)	417 (49.8)
12 years or more of education	74 (91.4)	103 (85.8)	491 (88.8)	682 (81.4)
White race	65 (80.3)	82 (68.3)	417 (75.4)	481 (57.4)
Type of Parkinson's Disease				
Akinetic-Rigid Case	195 (52.4)	..	1523 (51.1)	..
Tremor-Dominant Case	139 (37.4)	..	1096 (36.8)	..
Mixed-type Case	37 (9.95)	..	350 (11.7)	..
Relationship to Proband				
Parent	..	..	742 (24.9)	796 (26.7)
Sibling	..	..	1183 (39.7)	1151 (38.6)
Offspring	..	..	1055 (35.4)	1034 (34.7)
Family history of PD in first-degree relatives	54 (14.5)	38 (9.4)	..	..

* Values are indicated as number (percentage) of individuals unless otherwise specified. Age refers to age at diagnosis for cases and age at interview for controls.

** Controls were <=60 at the time of the interview.

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Table 2

Risk of AD and ET in All First Deg Relatives of Cases with PD by Type and Age of Diagnosis compared to Relatives of Controls.

	No. of Relatives	No. (%) of Relatives Affected	Hazard Ratio*	95% Lower Confidence Interval	95% Upper Confidence Interval	p- value**
Alzheimer's Disease						
Relative of Case	2980	37 (1.2)	1.02	0.64	1.64	0.93
Relative of Control	2981	35 (1.2)	1.0 referent			
Relative of Akinetic-Rigid Case***	1523	21 (1.4)	1.09	0.63	1.90	0.76
Relative of Tremor-Dominant/Mixed Case	1446	16 (1.1)	0.91	0.50	1.66	0.77
Relative of Control	2981	35 (1.2)	1.0 referent			
Relative of Younger Case (<=60)	553	11 (2.0)	2.86	1.44	5.71	0.003
Relative of Older Case (>60)	2427	26 (1.1)	0.77	0.46	1.30	0.33
Relative of Control	2981	35 (1.2)	1.0 referent			
Male Relative of Case	1548	15 (1.0)	1.08	0.51	2.26	0.84
Male Relative of Control	1504	14 (0.9)	1.0 referent			
Female Relative of Case	1432	22 (1.5)	1.00	0.54	1.84	1.00
Female Relative of Control	1477	21 (1.4)	1.0 referent			
Essential Tremor						
Relative of Case	2980	45 (1.5)	1.44	0.90	2.29	0.13
Relative of Control	2981	31 (1.0)	1.0 referent			
Relative of Akinetic-Rigid Case***	1523	18 (1.2)	1.06	0.59	1.91	0.85
Relative of Tremor-Dominant/Mixed Case	1446	25 (1.7)	1.69	0.99	2.88	0.05
Relative of Control	2981	31 (1.0)	1.0 referent			
Relative of Younger Case (<=60)	553	8 (1.4)	2.03	0.93	4.44	0.08
Relative of Older Case (>60)	2427	37 (1.5)	1.33	0.82	2.17	0.25
Relative of Control	2981	31 (1.0)	1.0 referent			
Male Relative of Case	1548	25 (1.6)	2.31	1.13	4.73	0.02
Male Relative of Control	1504	11 (0.7)	1.0 referent			
Female Relative of Case	1432	20(1.4)	0.97	0.52	1.83	0.92
Female Relative of Control	1477	20 (1.4)	1.0 referent			

*Cox Proportional Hazard Models, adjusted for sex, race and education

** P-value is a chi square p-value

*** One case proband (with 11 relatives) was excluded from the PD type analysis since he was "minimal signs of PD" at first PEG exam. He was AR in subsequent exams.

Table 2a

Sensitivity Analyses for risk of AD and ET in All First Deg Relatives of Cases with PD by Type and Age of Diagnosis compared to Relatives of Controls.

	No. of Relatives	No. (%) of Relatives Affected	Hazard Ratio*	95% Lower Confidence Interval	95% Upper Confidence Interval	p- value**
Analysis excluding 93 relatives with reported PD diagnosis, 6 with dual AD and PD diagnoses, 20 with dual ET and PD diagnoses.						
Alzheimer's Disease						
Relative of Case	2925	34 (1.2)	1.05	0.64	1.71	0.86
Relative of Control	2943	32 (1.1)	1.0 referent			
Relative of Younger Case (<=60)	537	9 (1.7)	2.95	1.39	6.28	0.01
Essential Tremor						
Relative of Case	2925	33 (1.1)	1.38	0.80	2.36	0.25
Relative of Control	2943	23 (0.8)	1.0 referent			
Relative of Younger Case (<=60)	537	6 (1.1)	2.15	0.87	5.32	0.10
*Analysis excluding 319 relatives of probands with low MMSE score****						
Alzheimer's Disease						
Relative of Case	2769	35 (1.3)	0.98	0.61	1.58	0.93
Relative of Control	2873	35 (1.2)	1.0 referent			
Relative of Younger Case (<=60)	553	11 (2.0)	2.81	1.41	5.59	0.00
Essential Tremor						
Relative of Case	2769	42 (1.5)	1.47	0.92	2.37	0.11
Relative of Control	2873	30 (1.0)	1.0 referent			
Relative of Younger Case (<=60)	553	8 (1.5)	2.02	0.92	4.43	0.08
Analysis including 54 relatives with "other dementia" in addition to those reported diagnosed with AD						
Alzheimer's Disease						
Relative of Case	2980	58 (2.0)	0.85	0.59	1.21	0.36
Relative of Control	2981	68 (2.3)	1.0 referent			
Relative of Younger Case (<=60)	553	17 (3.07)	2.40	1.40	4.12	0.00
Analysis excluding 324 relatives of PD probands diagnosed with "possible" PD at last PEG exam						
Alzheimer's Disease						
Parent of Case	2656	35 (1.3)	1.05	0.66	1.70	0.83
Parent of Control	2981	35 (1.2)	1.0 referent			
Parent of Younger Case (<=60)	512	10 (2.0)	2.67	1.30	5.48	0.01

	No. of Relatives	No. (%) of Relatives Affected	Hazard Ratio*	95% Lower Confidence Interval	95% Upper Confidence Interval	p- value**
Essential Tremor						
Parent of Case	2656	34 (1.3)	1.21	0.74	1.98	0.46
Parent of Control	2981	31 (1.0)	1.0 referent			
Parent of Younger Case (<=60)	512	6 (1.2)	1.56	0.65	3.77	0.32
Analysis with parents only						
Alzheimer's Disease						
Parent of Case	742	29 (3.9)	1.03	0.61	1.74	0.91
Parent of Control	796	29 (3.6)	1.0 referent			
Parent of Younger Case (<=60)	162	11 (6.8)	2.42	1.19	4.91	0.01
Essential Tremor						
Parent of Case	742	23 (3.1)	1.08	0.60	1.95	0.79
Parent of Control	796	23 (2.9)	1.0 referent			
Parent of Younger Case (<=60)	162	6 (3.7)	1.36	0.55	3.36	0.50

* Cox Proportional Hazard Models, adjusted for sex, race and education

** P-value is a chi square p-value

*** low score was less than 23 on the in-person MMSE, or less than 20 on the telephone version of the MMSE

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Table 3

Age at Diagnosis of AD, ET, PD and OD in Parents of Cases and Controls.

					T Test			
			95 % CI			95% CI		
Variables	**N**	**Mean**	**Lower Limit**	**Upper Limit**	**Mean difference**	**Lower Limit**	**Upper Limit**	**P-value***
AD Diagnosis age								
Parents of Controls	29	79.76	77.05	82.47	2.03	−1.36	5.43	0.23
Parents of Cases	29	77.72	75.56	79.89				
Mothers of Controls	20	80.85	77.33	84.37	2.79	−1.71	7.29	0.21
Mothers of Cases	17	78.06	75.18	80.94				
Fathers of Controls	9	77.33	72.90	81.77	0.08	−5.39	5.56	0.97
Fathers of Cases	12	77.25	73.41	81.09				
ET Diagnosis age								
Parents of Controls	20	69.25	64.71	73.79	8.85	0.63	17.07	0.04
Parents of Cases	20	60.40	53.21	67.59				
Mothers of Controls	12	68.67	61.74	75.60	2.44	−7.07	11.96	0.59
Motherss of Cases	9	66.22	58.97	73.47				
Fathers of Controls	8	70.13	63.30	76.95	14.49	0.06	28.92	0.03
Fathers of Cases	11	55.64	43.59	67.68				
PD Diagnosis age								
Parents of Controls	20	71.70	66.57	76.83	1.61	−5.25	8.47	0.63
Parents of Cases	33	70.09	65.60	74.58				
OD Diagnosis age								
Parents of Controls	30	78.40	74.24	82.56	−1.17	−6.60	4.27	0.65
Parents of Cases	23	79.57	76.29	82.84				

*P-values are Satterthwaite (unequal variance)