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Clinical Genetic Study of Familial Parkinson's Disease in Italy

*Paola Rossi, *Alberto Albanese, *Elena Moro,
†Maurizio Genvardi, and *‡Pietro Tonali

**Istituto di Neurologia, Università Cattolica del Sacro Cuore, Roma, Italy; †Istituto di Genetica, Università Cattolica del Sacro Cuore, Roma, Italy; and ‡CSS IRCCS, San Giovanni Rotondo, Italy.*

The role of genetic factors in the cause of idiopathic Parkinson's disease (IPD) has been controversial for many years. Familial studies have been hampered by lack of reliable diagnostic criteria and by incomplete awareness of genetic transmission in this common disorder when it occurred in more than one family member. There is growing evidence that genetic factors play a significant role in the susceptibility to IPD. A review of classic studies on IPD in twins, using strict clinical criteria and an appropriate statistical methodology, concluded that the genetic hypothesis can be neither proved or disproved (1). A later positron emission tomography (PET) study using ligands, such as fluorodopa in 17 twins, estimated a concordance of 45% in monozygotes and 29% in dizygotes, supporting the genetic hypothesis (2). The description of a large Italian kindred with an autosomal dominant model of inheritance and autopsy-proven Lewy bodies has given further support to the role of genetic factors (2). Linkage analysis of this Italian family has mapped a gene linked to 4q21-23 (3). The accurate description of a number of familial aggregations of typical IPD with a significant number of first-degree affected relatives and case-control studies have added support to the genetic hypothesis, establishing a broad consensus that a positive family history is one of the factors most consistently associated with IPD (4).

MATERIALS AND METHOD

Case-Control Study

Sixty-eight consecutive IPD patients and their spouses were evaluated between September 1995 and September 1996. All the patients were admitted to the

Gemelli Hospital, and the diagnosis of IPD was made according to the U.K. Parkinson's disease brain bank diagnostic criteria (5). Patients were classified as clinically definite IPD cases if they matched all such criteria; they were classified as clinically probable cases if they had some mild additional feature (e.g., dementia, dysautonomia). The spouses were studied in the outpatient clinic to evaluate the occurrence of neurologic symptoms, particularly parkinsonian signs. Spouses without evidence (even anecdotal) of parkinsonian signs were enrolled in the study as controls. Each couple (the patient and the spouse control) was submitted to a detailed interview to obtain information on the occurrence of parkinsonism among their relatives. The frequency of positive family history in patients and controls was measured using χ^2 and p statistics.

Clinical Genetic Study

All parkinsonian cases recorded at the Movement Disorders Clinic of the Gemelli Hospital until September 1996 were evaluated. Each patient was interviewed at least twice by an experienced neurologist and had to complete a detailed family questionnaire. In each family, at least two other members (a parent or another relative of the generation preceding that of the proband and a cousin or another relative of the same generation of the proband) were interviewed and also completed specific questionnaires. All family members who were identified as possibly affected by a movement disorder were personally visited whenever possible to be interviewed and completed a detailed questionnaire. In this manner, a family tree was constructed, and all suspected cases were evaluated when possible.

Patients were classified as clinically definite IPD, as non-IPD parkinsonian, or as not affected by a parkinsonian syndrome. Patients who were unavailable for the visit or were deceased were classified based on historical data as definite IPD, when the diagnosis was made by a neurologist expert in movement disorders; probable IPD, when the diagnosis was made by a neurologist not specialized in movement disorders; or possible IPD, when the diagnosis was made by a nonneurologist.

Segregation ratios were calculated using the Weinberg proband method and assuming single incomplete ascertainment of families. The age at onset and the year of onset correlations in pairs of IPD subjects were studied in each family with a linear regression analysis. A scattergram for age at disease onset and for year of onset of IPD in probands, compared with each affected relative, was constructed by using the linear regression coefficient and the Pearson correlation coefficient. To adjust for age-related incidence of IPD, the Kaplan-Meier survival analysis was applied. Ancestral relatives (excluding parents) were also analyzed (6).

RESULTS

Case-Control Study

The analysis confirmed the presence of a familial aggregation in a significantly higher percentage of consecutive IPD cases compared with controls ($\chi^2 = 10.12$, $p = 0.0015$, odds ratio = 4.94, 95% confidence interval = 1.38–2.47) (Table 24-1).

Clinical Genetic Study

A total of 789 IPD patients were on record at the Movement Disorders Clinic; 66 (8.3%) turned out to have at least one relative affected by a parkinsonian syndrome. This study deals with the first 48 of these patients.

Most of the families were Italian (Fig. 24-1); one family was from Lybia, and one was from Madeira. In 23 families, the affected members belonged to only one generation; in 25 families, multiple generations were affected. Overall, there were 48 index cases and 68 sec-

ondary cases, making a total of 116 affected members who were classified as clinically definite IPD.

In all families, patients with early-onset IPD (before 40 years) had a slightly higher proportion of affected siblings or parents than those with onset after 55 years; however, the number of early onset cases was too small for statistical analysis. Patients with tremor at onset were not more likely to have a high number of affected family members than those with bradykinesia at onset.

Clinical Features

The clinical features for all the families are shown in Tables 24-2, 24-3, and 24-4. When comparing multigenerational and monogenerational families, no significant differences were observed. Only when comparing families with one and those with two generations involved, a significant difference between the age at disease onset was observed ($p < 0.05$). Of a total of 25 multigeneration families, 27 affected subjects were females, 36 were males (21 with paternal and 15 with maternal transmission). In 16 probands, transmission was paternal; in 13 probands, it was maternal; and in 16, it was unknown. In the families of probands with paternal transmission, there were 25 affected male relatives and 16 affected females; in the families of probands with maternal transmission, there were 16 affected male relatives and 15 affected females. Overall, there were 12 cases with an affected parent; it was the father in seven cases (5 males and 2 females) and the mother in the case of 5 males. These features argue against an X-linked or a mitochondrial inheritance pattern.

The crude segregation ratios are shown in Table 24-5. No differences were observed between parents and siblings of probands in 48 families ($\chi^2 = 0.24$, $p = 0.62$, odds ratio = 0.78, 95% confidence interval = .5–1.319).

Overall, there were 34 affected ancestral relatives. They were all distributed unilaterally. This preponderance differs statistically from the 2 : 1 ratio predicted by the multigenic model and suggests a monogenic dominant inheritance.

A scattergram was constructed for age and year of disease onset in probands compared with each of their affected relatives. The linear regression coefficient for age at onset was $r^2 = 0.15$ ($p = 0.016$) and for calendar year of onset was $r^2 = 0.023$ ($p = 0.24$). The Pearson correlation coefficient for age was $r = 0.38$, and for the year of onset, it was $r = 0.15$. Correlation for proband-parent pairs for age at onset was $r^2 = 0.07$ ($p = 0.41$), and for year of onset, it was $r^2 = 0.32$ ($p = 0.068$). The Pearson correlation coefficient for age was $r^2 = -0.026$, and for year of onset, it was

TABLE 24-1. Case-control study: incidence of family history for a parkinsonian syndrome in IPD patients and in their spouses

Family history	IPD	Spouse controls	Total
Positive	22 (32.35%)	6 (8.82%)	28
Negative	46 (67.64%)	62 (91.17%)	108

IPD, idiopathic Parkinson's disease.



FIG. 24-1. The map shows the origins of the Italian families. The code for the province of origin is near each province's main town.

TABLE 24-2. Clinical features of families grouped by the number of generations containing affected cases

Feature	Total	One generation	Two generations	Three generations
Clinically or historically definite IPD cases (number)	116	54	55	7
Number of families	48	23	23	2
Average age at disease onset (years)	57.5	60.0 ^a	55.5 ^a	50.9
Disease duration (years)	10.7	9.3	11.9	17.4
Male female ratio	1.2			
Clinical presentation				
Tremor	66 (56.7%)	36 (66.7%)	29 (52.7%)	5 (71.4%)
Bradykinesia	23 (19.8%)	12 (22.2%)	10 (18.1%)	1 (14.2%)

IPD, idiopathic Parkinson's disease.

^aSignificantly different between each other ($p < 0.05$).

TABLE 24-3. Clinical diagnosis of Parkinson's disease in probands and affected relatives

IPD diagnosis	All	Probands	First degree	Other	Living
Clinically definite	63	47	11	5	59
Clinically probable	1	1	0	0	1
Historically definite	8	0	4	4	6
Historically probable	21	0	12	9	9
Historically possible	23	0	13	10	6
Total	116	48	40	28	84

IPD, idiopathic Parkinson's disease.

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TABLE 24-4. Number of families defined by the total number of affected members and the aggregation of cases within generations involved

Aggregation of cases	Two cases	Three cases	Four cases	Five cases
With cases in 1 generation	20	3	1	1
With cases in 2 generations	13	7	1	0
With cases in 3 generations	0	1	1	0
All families	33	11	3	1

TABLE 24-5. Segregation ratios

Parameter	All subjects	All >59 years
Affected sibs ^a	28	25
All sibs ^a	175	129
Segregation ratio	0.16	0.19
Standard error	0.04	0.04
Affected parents	12	12
All parents	96	96
Segregation ratio	0.078	0.084
Standard error	0.125	0.125

^aProbands excluded

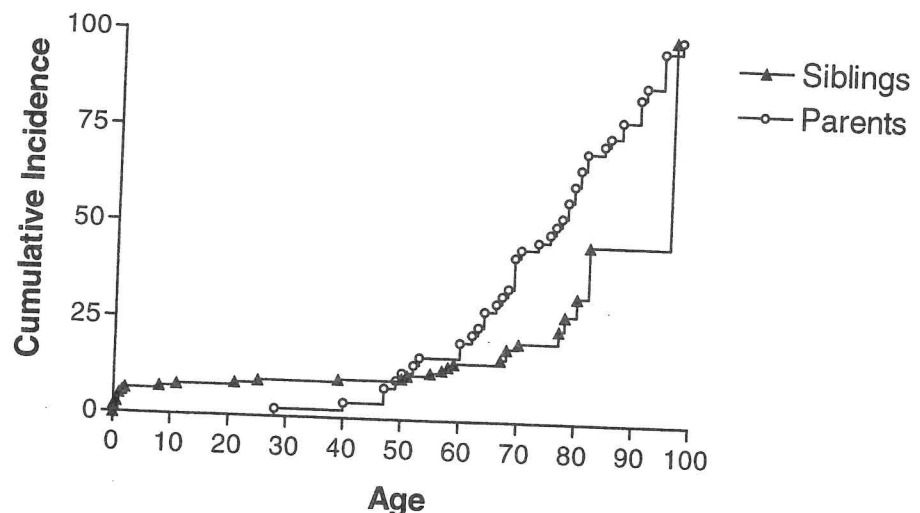
$r^2 = 0.057$. In proband-sibling pairs, correlation for age at onset was $r^2 = 0.38$ ($p = 0.0006$), and for year of onset, it was $r^2 = 0.026$ ($p = 0.43$). The Pearson correlation coefficient for age was $r = 0.62$, and for year of onset, it was $r = 0.16$. Taking all data together, the age at onset showed a significant intrafamilial correlation, which is stronger if only sib-sib pairs are considered. The year of onset does not show a significant intrafamilial correlation.

The ratio between affected sibs and all sibs showed that the proportion of affected sibs was 3.44% in families with an affected parent and 19.01% in families

without an affected parent. This points to a single gene rather than to a polygenic model.

Lifetime Cumulative Risk

The Kaplan-Meier lifetime cumulative risk was calculated. When the 48 families are considered together, nonproband siblings showed a lifetime risk of 0.21 ± 0.04 by age of 70. Among the parents, the risk is 0.45 ± 0.07 by age 70. This difference is significant (log rank $\chi^2 = 18.04$, $p < 0.0001$). The cumulative risk is shown in Figure 24-2.

**FIG. 24-2.** Kaplan-Meier lifetime cumulative risk is calculated for parents and siblings in 48 families.

DISCUSSION

Case-control studies have indicated a significantly increased risk of PD in first-degree relatives of patients with the disease; the maximum age-adjusted prevalence of IPD among such relatives approaches 20%. In an Italian study of 100 consecutive patients with PD and their spouse controls, a family history of IPD occurred in 24% of patients, compared with 6% of controls ($p < 0.001$) (7). If tremor alone was accepted as an inclusion criterion, the number of positive cases rose to 43%, compared with 9% in controls. In an English study, family history of IPD was positive in 26.8% of patients, compared with 14.8% of the controls (8), and in a North-American study (9), family history of IPD was positive in 16% of patients, compared with 4% of controls. In the first two studies, spouses served as controls; in the latter, first-degree relatives were used instead.

The subjects included in our study satisfied strict diagnosis criteria of Parkinson's disease and were indistinguishable from sporadic IPD patients ($p > 0.5$). Family members who presented only essential tremor were numerous in our families but were not included in the analysis.

Our data confirm the presence of familial aggregation in a significantly higher percentage of consecutive IPD cases compared with spouse controls. Family history was positive in 32.35% of patients, compared with 8.82% of controls, with an odds ratio of 4.9. Odds ratios between 3 and 5 indicate a significantly higher risk in parkinsonian families compared with controls. Taken together, these and previous data indicate that familial aggregation is significant and reflects a shared genetic, environmental, or mixed etiopathology. Our study also demonstrated the presence of intrafamilial correlation for age at disease onset, although not for year of disease onset. This argues against a shared acute environmental insult as an etiologic mechanism and is in accord with a prominent genetic role.

The expected ratio for dominant inheritance was 0.50, and for a recessive pattern, it was 0.25. In this study, crude segregation ratios were not statistically different for parents or siblings. This finding is consistent with an autosomal dominant transmission with reduced penetrance or with a multigenic model. One study (10) described 20 nonrandom families with at least two IPD-affected living relatives. Crude segregation ratios of 0.17 ± 0.04 and of 0.29 ± 0.07 , respectively, were calculated for siblings and parents of the multicase family probands. Ancestral relatives were all unilaterally distributed, and good correlation

emerged with age at onset, but not with year of onset, in couples of IPD relatives. Autosomal dominant inheritance of one or more genes with reduced penetrance was therefore proposed as the most likely model.

In a case-control study of 211 consecutive IPD cases, a significantly higher risk for siblings of cases with an affected parent was obtained (11). Crude segregation ratios were measured among 80 nonrandom multicase families and did not differ between siblings and parents. These observations are in keeping with our data and further support a model of dominant inheritance with reduced penetrance. Crude segregation ratios, as measured in this study, are also consistent with a model of autosomal recessive inheritance, predicting a risk of 0.25 for siblings without affected parents. Clinical features and crude segregation ratios, as measured in this study, were similar between siblings and parents. We observed only two cases of consanguinity.

Uncertainty between monogenic and multigenic inheritance exists in parkinsonian syndromes (8,12,13). A polygenic rather than a single gene model is preferable when the proportion of affected siblings is more than 2.5 times greater for cases with an affected parent than for those without. In our series, there were 12 probands with an affected parent and 36 without; the proportion of affected sibs was 3.44% in families with an affected parent and 19.01% in families with unaffected parents. This further points to a single gene rather than to a polygenic model. Ancestral cases of IPD relatives and their pairs were all unilaterally distributed, also suggesting a monogenic dominant model.

For diseases caused by only one gene, the intrafamilial correlation of age at onset is expected to be very high, with coefficients approaching unity. If different genes were responsible in different families, the age at onset would present a higher intrafamilial than interfamilial correlation. Correlation coefficients around 0.5 would be expected for a disease whose age at onset is controlled by one main gene plus other modifying genes; the coefficients would be even lower in the case of strong environmental influences on onset age. For our subjects, age at onset showed an intrafamilial correlation of 0.38, with a higher intrasibship correlation of 0.62. These data are compatible with the presence of a main gene associated with other genetic or nongenetic modifiers.

The lifetime cumulative incidence of IPD showed an increasing risk with age for parents or for siblings. The oldest cases occurred at age 96 for sib-

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lings and 97 for parents, with a cumulative risk approaching 0.01 for siblings and 0.01 for parents. The curve of cumulative risk for parents is moved to the right by about 30 years. In the only other study with a similar analysis (11), the lifetime cumulative risk was 0.42 for siblings and 0.45 for parents. Taken together, these observations provide strong support for autosomal dominant inheritance with age-related penetrance.

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Dopam Genetic Mecl Linkage S Ju

*Hiroto Matsumine, †
#Yasuhiro Yai

*Department
Bunkyo, Tokyo 113, Japan;
Niigata, Japan; †Nishiojiy
Tokyo Metropolitan
Hiroshin

The characteristic finding in P loss of dopamine cells in the : compacta (SNPC) with correspo the nigrostriatal dopamine systo dopa-responsive parkinsonism subgroup of familial juvenile usually before 40 years of age) by a good response to levodopa degeneration of the neurons in analysis of 13 families with this sponsible gene to markers on ch (1). This finding supports the molecular mechanism governir gral dopamine cells.

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