

SHORT REPORT

## Familial aggregation of Parkinson's disease in a Finnish population

Jaana M Autere, Jukka S Moilanen, Vilho V Myllylä, Kari Majamaa

**Abstract**

**Familial aggregation of Parkinson's disease in a Finnish population was investigated. A family history was obtained on 268 patients with Parkinson's disease and 210 controls ascertained from the population of the province of northern Ostrobothnia, Finland. Ten per cent of the probands reported an affected first degree relative, whereas the corresponding frequency was 3.8 per cent in the controls ( $p=0.01$ ). The relative risk of Parkinson's disease among the first degree relatives of the patients with Parkinson's disease was 2.9 (95 % confidence interval 1.3–6.4) and the cumulative incidence of Parkinson's disease by the age of 90 years was 3.3-fold higher among the first degree relatives of the patients than those of the controls. The crude segregation ratio was 0.27 for the siblings and 0.17 for the parents suggesting that recessive inheritance may be more common than dominant inheritance among Finnish patients with Parkinson's disease.**

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Parkinson's disease is a multifactorial disorder with an age dependent onset. Heritable factors contribute to the development of the disease and, after aging, a positive family history of Parkinson's disease seems to be the second most important risk factor for this disease.<sup>1,2</sup> Several large families with autosomal dominant inheritance of Parkinson's disease have been described.<sup>3–7</sup> Parts of these families harbour mutations in the  $\alpha$ -synuclein gene on chromosome 4,<sup>8</sup> but at least one additional gene is involved because linkage to a chromosomal locus 2p13 has been found among patients with autosomal dominant Parkinson's disease.<sup>9</sup> Furthermore, several mutations have been found in the parkin gene among patients with autosomal recessive early onset Parkinson's disease.<sup>10,11</sup>

Previous studies on familial aggregation of Parkinson's disease indicate a twofold to fivefold increased risk in relatives of affected members compared with relatives of unaffected members.<sup>12–16</sup> Crude segregation analyses have suggested an autosomal dominant rather than a recessive mode of inheritance among cases with a positive family history.<sup>12,17,18</sup> However, apart

from the few families with known pathogenic mutations, the genetic basis of Parkinson's disease is complex.

The Finnish population offers many advantages for studies on the genetic epidemiology of diseases. The population is homogenous in terms of cultural and environmental factors as well as genetic background. Furthermore, ascertainment of the patients is efficient as the health care is centralised and provided on a regional basis. We have carried out a family history study on patients with Parkinson's disease ascertained from a defined population in northern Finland to investigate the familial aggregation of Parkinson's disease and to test autosomal dominant and recessive models for the inheritance of Parkinson's disease in this population.

**Patients and methods**

PATIENTS AND CONTROLS

Patients were ascertained from the population of Northern Ostrobothnia, a province in northern Finland, with a population of 358 411 on the prevalence date 31 December 1996. In Finland there is universal access to health care and the population is assigned to publicly funded health services on a regional basis. Oulu University Hospital provides specialised medical care in the area, including neurological services. Furthermore, the cost of medications for Parkinson's disease is completely refunded by the National Health Insurance and, to obtain this refund, patients need written confirmation of their disease by a neurologist. A register of patients with newly diagnosed Parkinson's disease has been maintained at the Department of Neurology in the hospital since 1981 and provides a good representation of the incident cases of the disease in the population. This register was used to ascertain patients for this study. The diagnostic criteria of idiopathic Parkinson's disease were verified by chart review. The diagnosis of Parkinson's disease was made according to the criteria of the Parkinson's Disease Society Brain Bank.<sup>19</sup> A total of 328 patients were verified and included in this study.

A random sample of inhabitants of the province of Northern Ostrobothnia was obtained from the Central Population Registry of Finland. The inclusion criteria for controls were that they were born before the year 1950 and that they did not have Parkinson's disease.

Department of Neurology, University of Oulu, PO Box 5000, FIN-90014 University of Oulu, Finland

J Autere  
J Moilanen  
V Myllylä  
K Majamaa

University Hospital and University of Kuopio, PO Box 1777, FIN-70211 Kuopio, Finland

J Autere

Correspondence to: Dr Kari Majamaa kari.majamaa@oulu.fi

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*Clinical characteristics of patients with Parkinson's disease and controls interviewed for family history of Parkinson's disease*

	Patients		Controls
	Yes	No	Yes
Interview			
Men/Women (n)	133/135	26/34	103/107
Age (y)			
Men	68.9 (9.4)	74.2 (14.7)	61.6 (9.6)
Women	72.0 (9.5)	77.2 (7.8)	67.1 (10.9)
At onset	60.4 (10.7)	63.7 (11.8)	NA
At diagnosis	62.4 (10.6)	67.0 (11.0)	NA
At start of levodopa	62.9 (10.5)	67.5 (11.0)	NA

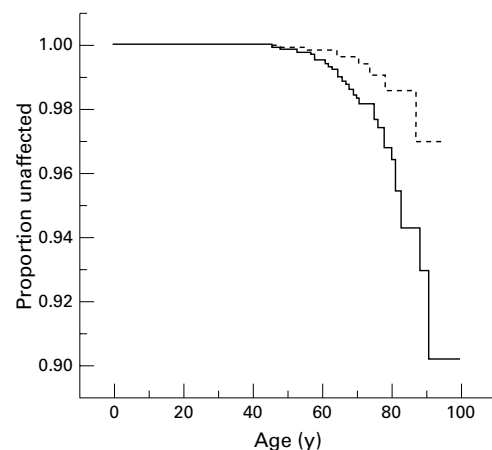
Values are means (SD); NA=not applicable.

#### COLLECTION OF INFORMATION ON FAMILY HISTORY

Family history information on the health status of the relatives was obtained from the patients with Parkinson's disease and the controls in a telephone interview. The persons to be contacted were informed about the investigation in a letter 1 to 2 weeks before the telephone interview. If the patient or control was unable to provide the information then a next of kin was interviewed. Information on sex, year of birth, year of death in case of deceased subjects, and history of Parkinson's disease, tremor, or any movement disorders was collected systematically concerning all first degree relatives, living or dead and regardless of age, including parents, siblings, and offspring. The place of birth of the parents was also requested. A positive family history was defined as the presence of Parkinson's disease in at least one first degree relative. Patient charts were reviewed to verify the reported diagnosis of Parkinson's disease among family members. The diagnosis of the disease in a relative was considered to be definite if the chart review confirmed the diagnosis or possible if the charts were not available and the diagnosis of Parkinson's disease was based only on the information from the proband.

#### STATISTICAL ANALYSIS

Kaplan-Meier survival analysis and log rank statistics were used to compare the age specific cumulative incidence of Parkinson's disease between first degree relatives of patients and controls. An independent samples *t* test and  $\chi^2$



*Proportion of first degree relatives remaining unaffected. Solid line, relatives of patients with Parkinson's disease; dotted line, relatives of the controls. Onset of Parkinson's disease in a relative, as reported by the proband, was defined as the end point. Unaffected relatives were censored at the age of death or at present age.*

analysis were used to determine differences between the cohorts. A crude segregation ratio was calculated as the ratio of affected persons to all persons in each group of relatives without ascertainment correction.

#### ETHICAL CONSIDERATIONS

The study was conducted with the permission of the ethics committee of the Medical Faculty, University of Oulu. Permission for chart review was obtained from the Finnish Ministry for Social Affairs and Health. Data on the controls were made anonymous after the information had been obtained.

#### Results

We interviewed by telephone 268 patients with Parkinson's disease and 210 controls for information on the health status of their first degree relatives. Sixty patients could not be interviewed, the mean age of this group being higher than that of the interviewed patients ( $p=0.02$  for men,  $p=0.001$  for women; table). The controls were younger than the patients ( $p<0.001$  for both sexes), but the mean age of the parents and siblings of the controls (60.6 (SD 18.4) years) was not significantly different ( $p=0.14$ ) from that of the probands (61.7 (SD 19.9) years).

Seventy seven per cent of the patients and 80% of the controls were born in Northern Ostrobothnia, 6% of both groups in other parts of northern Finland, and 17% of the patients and 14% of the controls elsewhere in Finland. Twenty seven patients (10%) reported Parkinson's disease among first degree relatives, whereas the corresponding frequency was 3.8% in the controls ( $p=0.01$ ). Twenty six of the probands reported an affected parent or sibling and one female proband had an affected daughter, this family being excluded from further analyses. The age at onset was 63.7 (SD 8.7) years in patients with familial Parkinson's disease and 60.0 (SD 10.8) years in those with sporadic disease ( $p=0.05$ ), but otherwise the clinical features of the 26 probands and the 242 sporadic patients did not differ. The 26 probands reported 29 affected siblings and parents. Review of the patient charts of the siblings disclosed 10 definite cases of Parkinson's disease, and the remaining 11 siblings and eight parents were left with a diagnosis of possible disease. The controls reported eight affected parents and siblings, of whom three were definite patients with Parkinson's disease and five had possible disease. The frequency of definite or possible Parkinson's disease was thus 1.6% in first degree relatives of the patients and 0.6% in first degree relatives of the controls. The relative risk of Parkinson's disease among the first degree relatives of the patients was 2.9 (95% CI 1.3–6.4).

Crude segregation ratio was 0.27 for the siblings and 0.17 for the parents. The age at death of the parents was not different between those families in whom affected members were found only among siblings and those families in whom affected members were present in two generations.

The age specific cumulative incidence of Parkinson's disease in 476 parents and 1149

siblings of the patients (figure) was significantly different from that in 394 parents and 907 siblings of the controls ( $p=0.009$ ). The cumulative incidence of disease by the age 90 years was 0.10 for parents and siblings of the patients and 0.03 for parents and siblings of the controls.

### Discussion

We identified patients with Parkinson's disease in a population based registry and found that 10% of the patients reported similarly affected first degree relatives. The controls were ascertained randomly from the population and, reflecting the homogeneity of the Finnish population, the patients and the controls did not differ in their basic demographic features. We found that the relative risk of Parkinson's disease was 2.9-fold higher and the cumulative incidence of disease by the age of 90 years was 3.3-fold higher among the first degree relatives of the patients than those of the controls. These figures are similar to those found previously in two other studies using population based cohorts<sup>13-16</sup> despite differences in case ascertainment, collection of family history information, and case verification. The similar frequency of positive family history and the similar risk among first degree relatives of probands suggest that the Finnish population does not differ from other populations in the frequency of familial Parkinson's disease.

Family history information on Parkinson's disease has been suggested to yield high sensitivity—that is, affected relatives are correctly classified—and high specificity—that is, unaffected relatives are correctly classified<sup>13</sup>—and, therefore, we did not attempt to verify cases that were reported to be healthy. Chart review of the cases reported to be affected showed that the rate of false positive reports was quite low indicating that the validity of the family history method in genetic epidemiology of Parkinson's disease is good. However, the family history method has some shortcomings compared with family studies as family history may lead to underestimation of the frequencies of the disorder in relatives<sup>20</sup> and family history data provided by patients may yield higher sensitivity than data obtained from unaffected subjects.<sup>21</sup>

Genetic epidemiological studies on Parkinson's disease have suggested autosomal dominant rather than recessive inheritance and the crude segregation ratios have been higher for parents than siblings<sup>2-12,17</sup> or equal.<sup>13-18</sup> Interestingly, the reverse was true in our study as the crude segregation ratio was 0.27 among the siblings of the probands and 0.17 among the parents. Furthermore, the ratio of families with affected members in a single generation to those with affected members in multiple generations was 1.25, whereas a ratio of 0.75 has been found elsewhere.<sup>22</sup> A single generation to multiple generation ratio exceeding unity may be considered to suggest a recessive inheritance. Parental consanguinity was not reported in our families, and the frequency of both parents being born in the same municipality was 55% for the parents of the controls, being similar to that of the parents of the probands and sporadic cases. We suggest that autosomal recessive inheritance partly

explains the segregation pattern seen in this study population. Patients with an early onset autosomal recessive Parkinson's disease have been shown to harbour mutations in the parkin gene.<sup>10-11</sup> Many different mutations have been found in this gene and they have been suggested to be the cause of the disease in one third of the families with autosomal recessive Parkinson's disease in Europe.<sup>11</sup> The entire Finnish population has grown from a small founder population and isolation of the population has led to enrichment of certain recessively inherited diseases, a phenomenon currently known as the Finnish disease heritage.<sup>23</sup> Our finding that autosomal recessive inheritance is plausible among Finnish patients with Parkinson's disease suggests that founder mutations in the parkin gene may be detectable in this population.

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