ORIGINAL ARTICLE

# Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland

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**Background:** The prevalence of sporadic and familial idiopathic pulmonary fibrosis (IPF) cases in Finland was evaluated according to the revised recommendations of the American Thoracic Society.
**Methods:** All Finnish pulmonary clinics (n=29) were included in the primary screening. Hospital data bases were used to identify patients with the diagnosis "alveolitis fibroticans idiopathica" (J84.1 in ICD-10 classification). The total number of patients with IPF was extrapolated based on the evaluation of random samples of case records in different centres. Families with more than one potentially affected member were identified from a questionnaire study and the diagnosis was verified from the medical records.
**Results:** Using this approach, the nationwide prevalence of IPF in Finland was estimated to be 16–18/100 000. In 90% of the patients lung involvement was assessed by high resolution computed tomographic (HRCT) scanning and in 31% a surgical biopsy specimen was available, further confirming the diagnosis. Seventeen multiplex families with 2–5 affected family members were identified, giving a prevalence of 5.9/million for familial IPF in Finland. Both multiplex and sporadic families were clustered in Eastern Finland. This clustering reflects the demographic history of Finland in the 16th century and suggests that multiplex families may share a common ancestor in the last 20–25 generations.
**Conclusion:** The familial form explained 3.3–3.7% of all Finnish cases of IPF diagnosed according to the revised international guidelines. Geographical clustering of multiplex families suggests a recent founder effect in patients with familial IPF.

Six original studies on the prevalence of clinical idiopathic pulmonary fibrosis (IPF) in different populations were identified using Medline (1966–2000). One of the prevalence estimates most frequently quoted in the literature is based on the Lung Program published in 1972 by the National Heart and Lung Institute in the USA.[1] During the years 1981–90 the prevalence of IPF in the Moravian and Silesian populations of the Czech Republic showed an increasing trend (from 7 to 12/100 000) with no predominance in either sex, the proportion of biopsy verified cases being 38%.[2] The most recent study reported a prevalence of IPF of 20/100 000 in men and 13/100 000 in women in New Mexico.[3] In this extensive epidemiological study, multiple sources were used to identify the patients and diagnosis was confirmed by clinical or necropsy data. Some studies have focused on patients exposed to fibrogenic dusts. In these studies the prevalence estimates for IPF have ranged from 3 to 6 per 100 000 in population based controls.[4–6]

In recent years it has become clear that patients with pulmonary fibrosis have different histological appearances and clinical presentations resulting from the heterogeneous nature of this group of inflammatory and interstitial fibrosing diseases. A new classification has identified four subtypes: acute interstitial pneumonia (AIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), and usual interstitial pneumonia (UIP).[7] Patients with IPF account for 60% of all patients with interstitial pneumonia and have a clinically progressive disease with the histological appearance of UIP.[8] In addition to histology, HRCT scanning has been shown to be an efficient tool for refining these histoclinical entities. In clinical practice, HRCT scanning is also safe for patients with an increased risk of surgical complications and identifies UIP with a high degree of confidence when interpreted in conjunction with the clinical findings.[9]

Since a marked variation in response to profibrotic agents has been found both in humans and in some animals, genetic predisposition is believed to play a role in the development of IPF. Although many candidate genes have been suggested, based on their role in inflammation and fibrosis, so far none of the contributing loci has been established. Association studies of polymorphisms in tissue antigens HLA-B and HLA-DR, interleukin 1 receptor antagonist, and tumour necrosis factor α genes are either conflicting or are at too early a stage and require further confirmation in other populations.[10 11] Families with several affected members can offer unique circumstances to explain specific molecular genetic mechanisms in the pathogenesis of the disease. Since 1950 many cases of familial IPF have been reported worldwide, as discussed in the online Mendelian Inheritance in Man database (http://www.ncbi.nlm.nih.gov/Omim/) and in the published literature.[10 12–15] These cases remained anecdotal, however, until Marshall and colleagues reported the prevalence of familial IPF (1.34 per million) in the UK, which accounted for a small proportion (0.5–2.2%) of all IPF cases. A possible genetic model for familial IPF is thought to be autosomal dominant with reduced penetrance but not, however, excluding an autosomal recessive pattern.[16]

In this study we report for the first time the nationwide prevalence of IPF in Finland diagnosed according to revised international guidelines. We also identify a number of Finnish families with two or more affected family members, implying that genetic factors might be of importance in the development of IPF. Strong clustering of these families in a certain area of Finland further suggests a founder effect among them.

## METHODS

### Patient selection

All pulmonary clinics (n=29) in Finland were contacted during the years 1997–8 to identify patients with IPF. Hospital

databases were screened for diagnosis J84.1 of the ICD-10 classification ("alveolitis fibroticans idiopathica"). To evaluate patients representing different parts of Finland, all five university hospitals, the two largest central hospitals, and the largest regional hospital were selected (group 1). The diagnosis was confirmed by a specialist in pulmonary medicine (UH) who visited these centres to review all the case records listed according to the patients' dates of birth. In each of the four central hospitals and in the one regional hospital a local specialist in pulmonary medicine evaluated all case records using the same criteria (group 2). In the remaining hospitals (group 3) the number of patients with IPF was extrapolated using statistics from group 1.

The study was approved by the ethical committees of the university hospitals and by the Ministry of Social Affairs and Health of Finland.

### Diagnostic criteria

The diagnosis of IPF was made in accordance with the international consensus statement[8] using the following major criteria: (1) exclusion of other known causes of interstitial lung disease; (2) abnormal pulmonary function with restriction and/or decreased transfer factor; (3) bibasal reticular abnormalities on HRCT scans or on conventional chest radiographs; and (4) bronchoalveolar lavage (BAL) or transbronchial lung biopsy not suggesting any other disease. Other minor criteria were: (1) age >50 years; (2) insidious onset of otherwise unexplained dyspnoea; (3) duration of illness >3 months; and (4) bibasal inspiratory crackles on auscultation. When a biopsy specimen was not available, all the major criteria and at least three of the four minor criteria had to be fulfilled. For patients with a surgical biopsy specimen showing UIP, only the major criteria were considered relevant.

### Identification of familial cases

To identify families with more than one affected member we mailed a questionnaire to all the patients identified in the primary screen who were still alive (n=1212) in which we asked whether there are or have been any other family members affected with a similar disease and for the names and birth places of their parents and grandparents; 675 (56%) replies were received. From the 88 patients who reported an affected family member, we asked for more detailed pedigree information and, with their permission, examined their medical records. In all confirmed multiplex families with living patients the affected family members had reported themselves independently to the study. If another affected family member(s) was already deceased, familial IPF was confirmed when medical data showed him/her to have fulfilled the diagnostic criteria. By using Finnish church records we traced back 3–5 generations of all identified families to confirm the origin of the family and to find possible links between pedigrees.

### Statistical analysis

All the information obtained from the questionnaires and medical records was stored and analysed using the Excel computer program. A two tailed Student's test was used to compare familial and sporadic IPF patients at the age of onset of the disease.

## RESULTS

### Prevalence

Hospital databases were used for primary screening of the study population. During the years 1997–8 we identified a total of 1445 inpatients or outpatients with the diagnosis J84.1 (alveolitis fibroticans idiopathica) in Finnish pulmonary clinics. The nationwide prevalence of IPF was computed using information from three identified patient groups (table 1). In eight centres (group 1) we evaluated a randomised sample of case records. These centres offered medical care to two thirds of all identified patients. In each of these hospitals we used the proportion of confirmed diagnoses to extrapolate the total number of IPF patients per centre. The percentage of confirmed diagnoses in different centres varied from 49% to 77%. This range of variation was then used to extrapolate the number of patients with IPF in group 3. In five centres a local pulmonary specialist evaluated all case records and confirmed the diagnosis for 113 patients (group 2). By combining these three groups we were able to identify a total of 833–943 IPF patients (table 1), equivalent to a prevalence of 16–18 per 100 000 in the Finnish population of 5.17 million. To detect possible bias caused by different data collection methods in different groups, we also computed the prevalence of IPF based solely on university hospital data retrieved by equivalent methods. Using this approach we identified a total of 370 patients per 2.07 million inhabitants, equivalent to a prevalence of 18 per 100 000 and concordant with the observed nationwide prevalence. No predominance of either sex was observed. The highest prevalence (45/100 000) was found in two sparsely populated hospital districts (174 700 inhabitants) in Eastern Finland (fig 1A).

According to the evaluated medical records, in 191 cases (71.8%) the diagnosis of IPF (n=266) was based on both major and minor clinical criteria. In most of these cases (n=164, 86%) lung involvement was assessed by HRCT scanning. In an additional 28.2% of cases the IPF diagnosis was

**Table 1** Total number of patients with IPF in Finland confirmed by extrapolation (groups 1 and 3) or by evaluation (group 2)

| Study groups | Primary screen diagnosis J84.1 | No of reviewed medical records | No of patients with IPF confirmed by evaluation | No of patients with IPF confirmed by extrapolation† | Total no of IPF patients in 3 study groups |
|---|---|---|---|---|---|
| Group 1 | | | | | |
| University 1 | 75 | 40 | 21 (53%) | 39 | |
| University 2 | 57 | 31 | 21 (68%) | 39 | |
| University 3 | 241 | 107 | 53 (50%) | 120 | |
| University 4 | 122 | 62 | 35 (56%) | 69 | |
| University 5 | 155 | 72 | 48 (67%) | 103 | |
| Central 1 | 99 | 39 | 21 (54%) | 54 | |
| Central 2 | 154 | 81 | 40 (**49%**) | 76 | |
| Regional 1 | 35 | 35 | 27 (**77%**) | 27 | |
| Total | 938 | 467 | – | 527 | 527 |
| Group 2 | | | | | |
| 5 centres | Not known | All | 113 | – | 113 |
| Group 3 | | | | | |
| 16 centres | 394 | None | (49–77%)* | 193–303 | 193–303 |
| Total | – | – | – | – | **833–943** |

*Range of variation between lowest and highest observed percentage shown in bold; †number of patients with diagnosis J84.1 corrected with the number of confirmed IPF diagnoses by evaluation.

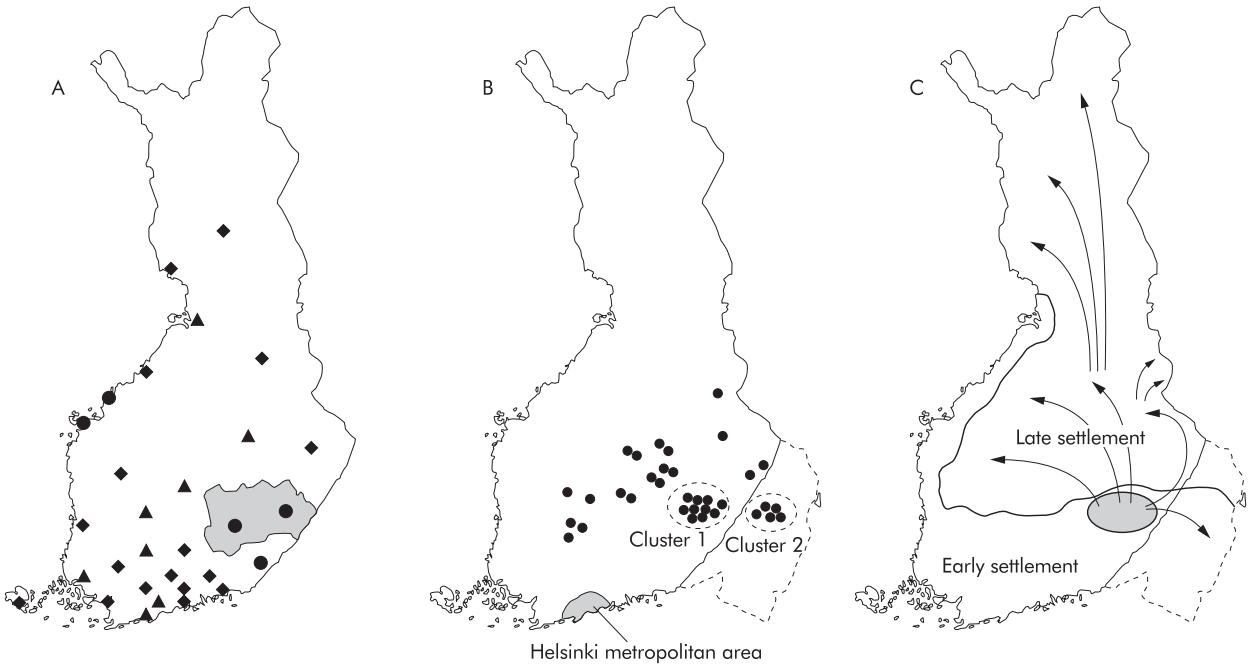


**Figure 1** Map of Finland showing (A) location of the Finnish pulmonary clinics (group 1=triangle, group 2=circle, group 3=diamond) and the region with the highest prevalence of sporadic IPF (shaded); (B) birth places of the parents of the multiplex families and the most densely populated Helsinki metropolitan area of Finland (1.2 million inhabitants); (C) settlement of the northern parts of Finland by internal migration during the 16th century (the province of Savo is shaded).

based on the major clinical criteria (n=75) and both HRCT scans and surgical biopsy specimens showing UIP were presented.

### Familial IPF

Eighty eight of the patients identified in the primary screen reported that they had or had had an affected family member. Based on medical records, in 17 families we were able to verify between two and five affected first degree family members (table 2). Diagnostic findings showed no difference in the clinical picture of IPF between familial and sporadic patients or shared exposures to known environmental risk factors for interstitial pneumonia. The age of onset was slightly lower among the familial cases than in the sporadic cases of IPF (mean 61.9 years *v* 65.3 years, p=0.11). Again, there was no predominance of either sex. Based on this approach, the prevalence of familial IPF was calculated as 5.9 per million (31 living patients at the time of the study).

To study the possible geographical distribution of multiplex families the birth places of the parents were examined (fig 1B). Most of the parents originated from Eastern Finland and were clustered in neighbouring municipalities. The most significant clustering (10 parents) was found in three rural sparsely inhabited municipalities (Tuusniemi, Heinävesi, and Kerimäki) in the province of Savo (cluster 1, fig 1B). These municipalities represent 0.3% of the present Finnish population (15 350 inhabitants). The second cluster of parents was found within 200 km in Karelia, a province that belonged to Finland before World War II. These five parents originated from another three neighbouring rural municipalities (Impilahti, Sortavala, and Ruskeala). The Finnish origin of the Karelian families (cluster 2) could be confirmed by their family names and their membership of the Lutheran church. By using parish records we have been able to trace each family back for 3–5 generations and have found that these families were already settled in these regions generations ago, but no obvious links between the pedigrees were identified.

**Table 2** Pedigree structures of the Finnish multiplex IPF families

| Pedigree | Affected family members | No of affected siblings in proband's sibship |
|---|---|---|
| 1 | Sibship | 5/13 |
| 2 | Sibpair | 2/3 |
| 3 | Sibship | 4/5 |
| 4 | Sibpair | 2/4 |
| 5 | Sibpair | 2/9 |
| 6 | Mother, her son and brother | |
| 7 | Mother-daughter | |
| 8 | Sibpair | 2/10 |
| 9 | Sibship | 4/8 |
| 10 | Sibpair | 2/6 |
| 11 | Sibship | 4/6 |
| 12 | Father-son | |
| 13 | Sibpair | 2/6 |
| 14 | Sibpair | 2/3 |
| 15 | Sibpair | 2/9 |
| 16 | Father-daughter | |
| 17 | Sibship | 3/8 |

## DISCUSSION

Using the international criteria for IPF,[8] we have evaluated the nationwide prevalence of sporadic and familial IPF in Finland. As a starting point, all potential patients were identified using hospital databases in which all diagnoses given to inpatients and outpatients are stored. Evaluation of case records showed that this approach was sensitive but highly non-specific; depending on the centre, 23–51% of the patients were excluded, most of whom had various interstitial lung diseases such as connective tissue disease related pulmonary manifestations, allergic alveolitis, bronchiolitis obliterans and organising pneumonia, eosinophilic pneumonia, asbestosis, and radiation therapy related or nitrofurantoin induced fibrosis. In clinical practice the diagnosis J84.1 had obviously been used as a primary diagnosis and then specified later in the diagnostic process when other causes for the symptoms and lung involvement were identified.

The evaluation also showed that the Finnish IPF patients are well characterised. In 90% the diagnosis was based on extensive clinical testing including assessment of lung involvement by HRCT scanning which has found to be the most efficient non-invasive method of distinguishing UIP from other interstitial pneumonias.[9 17] Twenty eight percent of IPF patients in our study had histological verification. Fifteen of 467 patients reviewed were excluded because the surgical biopsy specimen had a histological pattern other than UIP. Even though the revised international guidelines recommend that surgical biopsy specimens should be taken from all patients with suspected IPF and without contraindications to surgery, the clinical practice in Finland was found to be more conservative. According to the reviewed case records, biopsy specimens were mainly taken from patients with atypical features in the clinical outcome of the disease. The proportion of patients excluded is therefore probably too high to be considered a reliable estimate of the proportion of false positives among patients included without a biopsy. Nevertheless, most of the identified cases were histologically unverified, which may be a source of some uncertainty in the prevalence estimates. In addition, the selection of evaluated centres was not random but guaranteed that most of the case records were reviewed by a pulmonary specialist, minimising any possible bias on the final estimates. The accuracy of the reported nationwide prevalence was further supported by that reported by the university hospitals themselves. Since in Finland almost all patients with IPF are diagnosed and treated by a pulmonary specialist, we can assume that the proportion of false negatives is negligible. The prevalence of IPF has varied in previous surveys, showing in the most recent studies—including ours (16–18 per 100 000)—an increasing trend. However, the increase may be explained, at least partly, by improved diagnostic methods and aging of the population. In contrast to some previous findings, we found no male predominance among the patients.

Familial and sporadic IPF are clinically and histologically indistinguishable, suggesting that the same signalling pathways may be affected in both forms of the disease.[10] By discovering any genetic defects in familial IPF, we might also therefore detect genetic defects predisposing to the sporadic form. We were able to identify 17 multiplex families, each with 2–5 affected family members. The prevalence of 5.9/million for familial cases among the Finnish population is four times higher than that reported in the UK and accounted for 3.3–3.7% of IPF cases in Finland. In our study the identification of multiplex families was based solely on questionnaires. Although the rather low response rate can be explained by dilution of the target group recognised in the primary screen, it is possible that we have missed some familial cases and are therefore still underestimating the prevalence of familial IPF. Most families were characterised by affected siblings, while only three parent/offspring pairs were detected. The family structures of the data set, however, may be biased towards sibling pairs since, in some cases, the possibly affected parent had died so long ago that it made verification of the diagnosis in accordance with our criteria impossible.

An exceptional population history has had a great impact on genetic disorders among the Finnish population.[18–20] Given the fact that recent founder effects have offered unique opportunities for gene mapping strategies among Finnish patients, we studied the origin of the multiplex IPF families in more detail.[21 22] Interestingly, familial cases showed particularly strong clustering in Eastern Finland (fig 1). After Finland was permanently inhabited about 2000 years ago, the population remained small and isolated in the coastal regions for many centuries (fig 1C). These regions are still the most densely populated areas in Finland. During the 16th century the rest of the country was slowly settled by internal migration (late settlement). For political and economic reasons, this internal migration started almost exclusively from the province of Savo (fig 1C), the region where the largest cluster of familial IPF parents was observed (cluster 1). Although most of the migrants moved slowly towards the north and north west, there was also migration to the east, particularly to Karelia. Once settlements of 40–60 founding families were established, they expanded in isolation forming sub-isolates. Rapid expansion of the population starting at the beginning of the 18th century led to the enrichment of several recessive genes in these regional isolates. As expected, molecular genetic studies have found a major mutation among these patients and, in some cases, genealogical studies have even revealed the common ancestor and linked pedigrees together several generations ago.[21 22]

Half of the families with IPF were found in two clusters located in close proximity (fig 1B). According to the genealogical information available, some of the families had settled into these regions more than 10 generations ago. It was therefore not surprising that we were unable to prove specific genealogical ties between the families because we were only able to trace them back to the beginning of the 19th century. In none of the families was a history of exposure to any known environmental risk factors for pulmonary fibrosis found. The strong clustering of the ancestors of the patients therefore supports the importance of genetic factors over shared environmental factors in the development of IPF.

In conclusion, by combining demographic knowledge of the history of the Finnish population and the geographical distribution of the multiplex families, it is plausible to conclude that the families shared a common ancestor before migration started from the province of Savo. During the migration the ancestral disease causing allele spread into the late settlement regions but could not be found in the early settlement region.

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