Clinical and Pathologic Features of Familial Interstitial Pneumonia

Mark P. Steele, Marcy C. Speer, James E. Loyd, Kevin K. Brown, Aretha Herron, Susan H. Slifer, Lauranell H. Burch, Momen M. Wahidi, John A. Phillips III, Thomas A. Sporn, H. Page McAdams, Marvin I. Schwarz, and David A. Schwartz

Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Department of Pathology, Department of Radiology, and Center for Human Genetics, Duke University Medical Center and VA Medical Centers, Durham, North Carolina; Vanderbilt University School of Medicine, Nashville, Tennessee; and National Jewish Medical and Research Center and University of Colorado Health Sciences Center, Denver, Colorado

Rationale: **Several lines of evidence suggest that genetic factors and environmental exposures play a role in the development of pulmonary fibrosis.**

Objectives: **We evaluated families with 2 or more cases of idiopathic interstitial pneumonia among first-degree family members (familial interstitial pneumonia, or FIP), and identified 111 families with FIP having 309 affected and 360 unaffected individuals.**

Methods: **The presence of probable or definite FIP was based on medical record review in 28 cases (9.1%); clinical history, diffusing capacity of carbon monoxide (D_{LCO}), and chest X-ray in 16 cases (5.2%); clinical history, D_{LCO}, and high-resolution computed tomography chest scan in 191 cases (61.8%); clinical history and surgical lung biopsy in 56 cases (18.1%); and clinical history and autopsy in 18 cases (5.8%).**

Results: **Older age (68.3 vs. 53.1; $p < 0.0001$), male sex (55.7 vs. 37.2%; $p < 0.0001$), and having ever smoked cigarettes (67.3 vs. 34.1%; $p < 0.0001$) were associated with the development of FIP. After controlling for age and sex, having ever smoked cigarettes remained strongly associated with the development of FIP (odds $ratio_{adj}$, 3.6; 95% confidence interval, 1.3–9.8). Evidence of aggregation of disease was highly significant ($p < 0.001$) among sibling pairs, and 20 pedigrees demonstrated vertical transmission, consistent with autosomal dominant inheritance. Forty-five percent of pedigrees demonstrated phenotypic heterogeneity, with some pedigrees demonstrating several subtypes of idiopathic interstitial pneumonia occurring within the same families.**

Conclusions: **These findings suggest that FIP may be caused by an interaction between a specific environmental exposure and a gene (or genes) that predisposes to the development of several subtypes of idiopathic interstitial pneumonia.**

Keywords: cigarette smoking; familial pulmonary fibrosis; genetics; pulmonary fibrosis

Pulmonary fibrosis is a general term used to describe the group of fibrosing interstitial lung diseases that causes progressive scarring of the alveolar interstitium, often leading to hypoxemic respiratory insufficiency. Pulmonary fibrosis can result from environmental exposures, such inhalation of fibrogenic dusts or aerosolized organic antigens; drug toxicity; or systemic diseases; or occur as an isolated, sporadic disease without extrapulmonary involvement (idiopathic interstitial pneumonia). Idiopathic interstitial pneumonias (IIPs) are composed of several subtypes of pulmonary fibrosis including idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia, and acute interstitial pneumonia. These types of IIP differ in clinical, radiographic, and histopathologic features, with IPF by far the most common (1, 2).

Four lines of evidence suggest that the development of pulmonary fibrosis is, at least in part, determined by genetic factors. First, the familial clustering of pulmonary fibrosis, an uncommon disease, has been reported in monozygotic twins raised in different environments (3–5), in genetically related members of several families (5–8), in consecutive generations in the same families (5, 9, 10), and in family members separated at an early age (7). Although a single report suggests that familial interstitial pneumonia (FIP) is inherited as an autosomal recessive trait (11), other pedigrees demonstrate an autosomal dominant pattern of inheritance (7, 12, 13), perhaps with reduced penetrance (3, 4, 6–8, 12, 14, 15). Second, pulmonary fibrosis is observed in genetic disorders with pleiotropic presentation, including Hermansky-Pudlak syndrome (16), neurofibromatosis (17), tuberous sclerosis (18, 19), Niemann-Pick disease (20), Gaucher disease (21), familial hypocalciuric hypercalcemia (22), and familial surfactant protein C mutation (23). Third, considerable variability exists in the development of pulmonary fibrosis among workers exposed to similar concentrations of fibrogenic dusts or organic antigens. For instance, after exposure to asbestos, similarly exposed individuals may experience different outcomes (24, 25). Fourth, inbred strains of mice differ in their susceptibility to fibrogenic agents. In comparison with BALB/c or 129 mice, C57BL/6 mice develop more lung fibrosis when challenged with either bleomycin (26, 27) or asbestos (28, 29).

To investigate the genetic and environmental determinants of pulmonary fibrosis, we evaluated 111 families with a diagnosis of an IIP in at least two affected relatives within three degrees of relationship (FIP), identifying 309 affected and 360 unaffected individuals. Our results demonstrate phenotypic heterogeneity of IIP in 45% of the families, with an independent effect of cigarette smoking on its expression within at-risk families.

METHODS

Family Recruitment

We used web-based advertising of our study (www.fpf.duke.edu/ and http://www.nhlbi.nih.gov/studies/fibrosis/) and direct mailings to physician members of the American Thoracic Society (ATS) to identify

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Correspondence and requests for reprints should be addressed to Mark P. Steele, M.D., Box 3171, Duke University Medical Center, Durham, NC 27710. E-mail: mark.steele@duke.edu

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potential families. In addition, a toll-free number, 877-587-4411, was established for subject recruitment.

Family, Ascertainment, and Phenotyping

Three sites in the United States (National Jewish Medical and Research Center, Denver, CO; Vanderbilt University, Nashville, TN; and Duke University Medical Center, Durham, NC) were established to identify subjects with FIP, and to enroll and phenotype probands and family members. The study was approved by the institutional review boards of the respective institutions and a certificate of confidentiality was obtained from the National Institutes of Health (Bethesda, MD). After informed consent was obtained, all subjects were asked to complete a detailed health and environmental exposure questionnaire, and to undergo chest radiography (posteroanterior and lateral) and carbon monoxide diffusing capacity (D_{LCO}) measurement at a local health facility. Dyspnea was assessed as described in the ATS-DLD-78 questionnaire (*see* the online supplement) (30). Those subjects who had unexplained dyspnea of grade 2 or greater, an abnormal chest radiograph suggestive of ILD, or a D_{LCO} less than 80% predicted, and those subjects who self-reported a diagnosis of ILD, underwent a high-resolution computed tomography (HRCT) scan of the chest in the prone and supine positions. All radiologic images were forwarded to Duke University and independently interpreted by two investigators (M.P.S. and D.A.S.) who were blinded to the clinical history. Standard criteria (1, 2, 31) were used to establish the diagnosis of IIP and inconsistencies between the individual readers were resolved by consensus, using a third reader (H.P.M.). Subjects with an HRCT scan suggestive of IIP were recommended to undergo a surgical lung biopsy. All phenotype data, including questionnaires, relevant medical history, digitized radiographic images, and lung function measurements, were entered into PEDIGENE (32), a secure, coded database.

Classification of Affected and Unaffected Individuals with Pulmonary Fibrosis

For the purposes of this study, a diagnosis of FIP required the presence of two or more cases of probable or definite IIP in individuals related within three degrees. We used criteria established by the American Thoracic Society and European Respiratory Society to guide the classification of patients with ILD (1, 2). Diagnostic categories included unaffected, possibly affected, probably affected, and definitely affected. *Unaffected* was defined as no evidence of interstitial lung disease on chest radiograph, a D_{LCO} of or exceeding 80% predicted, and a dyspnea level of 0 or 1 according to the ATS dyspnea scale. *Definitely affected* was defined as either surgical lung biopsy or autopsy evidence of an IIP with an appropriate clinical history. Lung biopsy samples were classified by one of us (T.A.S.) according to revised criteria for the diagnosis of IIPs (2). *Probably affected* was defined as bilateral reticular abnormalities associated with honeycombing on HRCT scan. If honeycombing was absent, bibasilar reticular abnormalities, with or without ground glass opacities in the absence of other explanations for interstitial abnormalities (1, 31) on HRCT scan, plus either dyspnea of grade 2 or greater or a D_{LCO} less than 80%, also met the definition. *Possibly affected* was defined as those subjects with chest radiographs suggestive of ILD but who did not undergo additional testing to establish a more certain diagnosis. *Indeterminate* was used for those subjects for whom the investigators thought the technical quality of the data was unreliable. For deceased subjects, medical records, radiology reports, autopsy reports, archived lung biopsy slides, and pathology reports were jointly reviewed by study investigators (M.P.S. and D.A.S.) and classified using the best available evidence.

Statistical Considerations

For all analyses, we included only subjects who were phenotyped as unaffected or probably/definitely affected; possibly affected and indeterminate subjects were excluded from all comparisons. As a proxy for age at onset, age at diagnosis was defined as the earliest date of the first abnormal chest X-ray, HRCT scan, or lung biopsy. Univariate comparisons were made on the basis of standard statistical approaches (χ^2 test and Student *t* test with a two-tailed distribution). The intraclass correlation between siblings for age at diagnosis and for smoking status was calculated according to the familial correlation (FCOR) module of the SAGE (Statistical Analysis for Genetic Epidemiology) program (33).

We used a family-based case-control approach to evaluate the potential independent relationship between cigarette smoking and FIP. This approach was implemented by means of a conditional logistic regression model in which case and control subjects were matched by sibship to account for familial correlations (34). All sibships (n = 79) that included at least one affected family member and one unaffected sibling control with historical smoking data were included in the analysis; the analysis was also performed with only those unaffected siblings who were older than the youngest age at diagnosis of an affected sibling (n = 39). Smoking history was defined according to standard criteria to identify never, former, and current cigarette smokers. In our multivariable model, we included sex and age at diagnosis to fully evaluate the independent relationship between cigarette smoking and IIP.

Evidence in support of a genetic component for FIP was evaluated by two methods. First, familial aggregation was assessed by testing for lack of independence in affection status among sibling pairs within the probable/definite diagnostic classifications. Second, pedigrees were inspected for classic patterns of Mendelian transmission.

RESULTS

We identified 111 families who met our case definition of FIP; within these families, 417 self-reported as unaffected and 291 self-reported as affected (Table 1). For the familial cases, we used a sequential sampling strategy in which all first-degree relatives (adults) of cases are asked to participate in the study. Of potential family members who were approached, 237 (25%) declined to participate. Because of institutional review board restrictions, we have neither clinical nor questionnaire data concerning these nonparticipants. The types of data collected with self-report status are shown in Table 1. Either a questionnaire, D_{LCO}, or radiographic study (chest X-ray or HRCT scan) was obtained in 97.4% of the subjects, and 92.5% of the subjects had at least two of these three evaluations (questionnaire, D_{LCO}, or radiographic study).

After extensive clinical evaluation, we determined that 360 were unaffected, 309 were found to have definite or probable FIP, and 44 were found to have possible FIP (Table 2). Nine individuals had an indeterminate diagnosis. Fifty-two of the 111 families had at least one case of surgical lung biopsy-proven, definite interstitial pneumonia. In aggregate, the diagnosis of probable or definite FIP was based on medical record review in 28 cases (9.1%); clinical history, D_{LCO}, and chest X-ray in 16 cases (5.2%); clinical history, D_{LCO}, and HRCT scan in 191 cases (61.8%); clinical history and surgical lung biopsy in 56 cases (18.1%); and clinical history and autopsy 18 cases (5.8%; Table 2). Of those classified as probable or definite FIP, the diagnosis based on HRCT scan or histopathologic pattern was most consis-

TABLE 1. CLINICAL DATA COLLECTED ACCORDING TO SELF-REPORT CATEGORIES

	Self-Report Status		
Data Obtained	Unaffected (*n = 417*)	Affected (*n = 291*)	Unknown (*n = 14*)
Questionnaire	403 (96.6)	217 (74.6)	10 (71.4)
D_{LCO}	349 (83.7)	223 (76.6)	5 (35.7)
Chest X-ray	395 (94.7)	168 (57.7)	12 (85.7)
High-resolution CT chest scan	112 (26.9)	228 (78.4)	7 (50.0)
Transbronchial biopsy	0 (0.0)	31 (10.7)	2 (14.3)
Surgical lung biopsy	3 (0.7)	81 (27.8)	1 (7.1)
Autopsy confirmed	2 (0.5)	17 (5.8)	0 (0.0)

Definition of abbreviations: CT = computed tomography; D_{LCO} = carbon monoxide diffusing capacity.

Percentages are shown in parentheses.

TABLE 2. CLINICAL EVALUATION USED TO IDENTIFY AFFECTION STATUS

	Consensus Affection Status			
Clinical Evaluation	Unaffected (*n = 360*)	Possible (*n = 44*)	Probable (*n = 231*)	Definite (*n = 78*)
Medical record*	14 (3.9)	5 (11.4)	22 (9.5)	6 (7.7)
Clinical history, D_{LCO}, and CXR†	281 (78.1)	21 (47.7)	16 (6.9)§	0
Clinical history, D_{LCO}, and HRCT scan‡	64 (17.8)	18 (40.9)	191 (82.7)‖	0
Surgical lung biopsy	0	0	0	56 (71.8)
Autopsy	1 (0.3)	0	2 (0.9)	16 (20.5)

Definition of abbreviations: CXR = chest radiograph; HRCT = high-resolution computed tomography; D_{LCO} = carbon monoxide diffusing capacity.

Nine patients had an indeterminate consensus diagnosis and are not included. Percentages are shown in parentheses.

* "Medical record" represents review of clinical evaluations, radiology reports, autopsy reports, archived lung biopsy slides, and pathology reports. These records were jointly reviewed by study investigators (M.P.S. and D.A.S.) and independently classified on the basis of the best available evidence.

† Fifty-three patients did not have a D_{LCO} measurement, and 1 patient had surgical lung biopsy indicating interstitial lung disease (ILD) by report; however, we were unable to locate and review the biopsy material.

‡ Eighteen patients did not have a D_{LCO} measurement.

§ Nine patients had extensive bilateral, basilar, and peripheral honeycombing on CXR with low lung volumes and D_{LCO} less than 50% predicted, and seven patients had bilateral, basilar, and peripheral honeycombing on CXR with low lung volumes but without a D_{LCO} available.

‖ Fourteen subjects had a surgical lung biopsy indicating ILD by report; however, we were unable to locate and review the biopsy.

tent with IPF/UIP in 248 cases (80.2%), NSIP in 20 cases (6.4%), COP in 2 cases (0.6%), and centrilobular nodules in 1 case (0.3%), and 38 cases (12.3%) had an unclassifiable form of interstitial pneumonia (Table 3). Of those classified as definite FIP based on histopathologic pattern (n = 78), the diagnosis was IPF/UIP in 67 cases (85.6%), NSIP in 8 cases (10.25%), COP in 2 cases (2.5%), and unclassified in 1 case (1.3%), which is a similar distribution compared with probable FIP assessed by clinical history, D_{LCO}, and HRCT scan.

Of 417 subjects initially self-reported as unaffected, 1.4% (n = 6) met the consensus diagnosis of indeterminate, 6.7% (n = 28) met the consensus definition of possible FIP, and 7.9% (n = 33) met the consensus definition of probable or definite FIP. Of the 291 subjects who initially self-reported as affected, 0.7% (n = 2) met the consensus diagnosis of indeterminate, 1% (n = 3) met the consensus definition of unaffected, and 4.8% (n = 14) met the consensus definition of possible FIP. For probable or definite FIP, the sensitivity, specificity, and accuracy of self-reported affected status were 89.2, 95.7, and 92.8%, respectively. The positive predictive value and negative predictive value of self-reported affected status were 94.1 and 92%, respectively. For individuals self-reported as unaffected with a consensus diagnosis of probable or definite FIP (n = 33), there were 20 patients with features of probable IPF/UIP, 2 with features of probable NSIP, 4 with definite IPF/UIP, and 7 with unclassifiable FIP.

TABLE 3. IDIOPATHIC INTERSTITIAL PNEUMONIA SUBTYPES AMONG PROBABLE AND DEFINITE CASES OF FAMILIAL INTERSTITIAL PNEUMONIA

	Probable (*n = 231*)	Definite (*n = 78*)
IPF/UIP	181 (78.4)	67 (85.9)
NSIP	12 (5.2)	8 (10.3)
COP	0	2 (2.6)
Centrilobular nodules	1 (0.4)	0
Unclassified ILD	37 (16.0)	1 (1.3)

Definition of abbreviations: COP = cryptogenic organizing pneumonia; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

Percentages are shown in parentheses.

Within the 111 families, we found that older age (68.3 vs. 53.1 yr; $p < 0.0001$) and male sex (55.7 vs. 37.2%; $p < 0.0001$) were associated with the presence of FIP (Table 4). Whereas older age may simply reflect the demographics of IIP, the age range of disease onset is quite broad (30.3–95.4 yr) and the frequency distribution of age at diagnosis demonstrates a group of younger affected subjects (Figure 1), although the evidence of bimodality in age at diagnosis is nonsignificant. Moreover, age at diagnosis was highly correlated (intraclass correlation, 0.78; $p < 0.01$) among affected siblings, suggesting a genetic basis for the age of onset of this disease. Male sex was associated with the presence of FIP (55.7 vs. 37.2%; $p < 0.0001$), although age at diagnosis did not differ significantly between males and females ($p > 0.20$).

Within the 111 families, we found that a history of ever cigarette smoking (67.3 vs. 34.1%; $p < 0.0001$) was associated with the presence of FIP (Table 4). The association was similar for either probable (odds ratio, 4.0; $p < 0.00001$) or definite (odds ratio, 3.7; $p < 0.00001$) FIP (Table 5). After controlling for age and sex, ever cigarette smoking remained strongly associated with the presence of FIP (odds ratio_{adj}, 3.6; 95% confidence interval, 1.3–9.8; Table 5). When the analysis was limited to include unaffected siblings only when they were older than the youngest age at diagnosis of an affected sibling, the results were nonsignificant; however, the small sample size (n = 39) indicates that power to detect a significant difference is small. Furthermore, the correlation of smoking in affected siblings was not significant (intraclass correlation, 0.25; $p = 0.10$), indicating that smoking status is not correlated among affected siblings, and that even among cigarette smokers, genetic susceptibility plays an important etiologic role in the development of this disease. We did not identify a relationship between the number of pack-years of cigarette smoking and the age at diagnosis.

Among patients with either probable (n = 231) or definite (n = 78) FIP, subjects with definite FIP were significantly ($p = 0.006$) younger at diagnosis than subjects with probable FIP (Table 6). In addition, subjects with definite FIP died at a younger age ($p = 0.02$), had higher mortality ($p < 0.0001$), and had a shorter time to death from age at diagnosis ($p = 0.02$) when compared with subjects with probable FIP (Table 6). Interestingly, 21.9% of patients with probable FIP and 28.2% of

TABLE 4. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY AFFECTION STATUS IN FAMILIAL INTERSTITIAL PNEUMONIA

Demographic and Clinical Characteristics	Consensus Diagnosis: Unaffected (*n = 360*)	Consensus Diagnosis: Probable or Definite FIP (*n = 309*)
Subjects self-reported as affected, no. (%)	3 (0.8)	272 (88.0)
Subjects self-reported as unaffected, no. (%)	350 (97.2)	33 (10.7)
Subjects self-reported as unknown, no. (%)	7 (1.9)	4 (1.3)
Male, no. (%)	134 (37.2)	172 (55.7)†
Age, yr, mean ± SD	53.1 ± 11.4	68.3 ± 11.0†
Range	31.8–91.1	30.3–95.4
Median	50.9	70.0
Age at diagnosis, yr, mean ± SD*	NA	66.6 ± 11.0
Range	NA	29.8–94.4
Median	NA	68.8
Mortality: deaths, no. (%)	5 (1.4)	150 (48.5)†
Age at death, yr, mean ± SD	66.0 ± 8.3	67.5 ± 10.5
Range	60.2–71.9	35.8–87.9
Median	NA (n = 2)	68.4
Time to death from age at onset, yr, mean ± SD	NA	1.5 ± 1.9
Smoking history, no.	346	232
Current smoker, no. (%)	34 (9.8)	18 (7.8)†
Former smoker, no. (%)	83 (24.0)	138 (59.5)†
Never smoker, no. (%)	228 (65.9)	76 (32.8)†
Pack-yr, mean ± SD	6.9 ± 14.7	16.6 ± 21.0†
Pack-yr, range (median)	0–82.0 (0)	0–103.5 (9.6)

Definition of abbreviations: FIP = familial interstitial pneumonia; NA = not applicable.
Individuals classified as possible FIP are not included.
* Age at diagnosis is defined as the earliest date of first abnormal chest X-ray, high-resolution computed tomography, or lung biopsy.
† $p < 0.0001$.

patients with definite FIP reported no dyspnea, further suggesting that screening pulmonary function measurements and radiographic studies are important in determining affected status within these families.

Although 61 families (54.9%) had uniform radiographic and/or histopathologic features of IPF/UIP among the affected individuals, 50 families (45.1%) demonstrated radiographic and/or histopathologic features consistent with more than one type of IIP among affected individuals (*see* Figure E1 in the online supplement). Of the heterogeneous families with only two types of disease, 58.3% included both unclassified ILD and IPF/UIP and 35.4% included both NSIP and IPF/UIP. Other combinations of disease found in single pedigrees included surgical lung biopsy-proven UIP and COP (pedigrees VAF44 and DUK196) and UIP with an RB-ILD–like pattern on HRCT scan, having centrilobular nodules and ground glass highly atypical of UIP/IPF (VAF47). Although most families demonstrated only two forms of the disease, two families had more complex mixtures. DUK164 included one affected individual with an HRCT scan consistent with IPF, another with probable NSIP on HRCT scan characterized by ground glass and reticulation without honeycombing, and a third with an HRCT scan having RB-ILD–like features characterized by centrilobular nodules and ground glass. None of the family members in DUK164 had a history of tobacco smoking or reported environment exposures. The effect of smoking was similar in both the clinically uniform families and the families with clinical heterogeneity ($p > 0.50$).

The 111 pedigrees have an average size of 10.8 ± 6.9 individu-

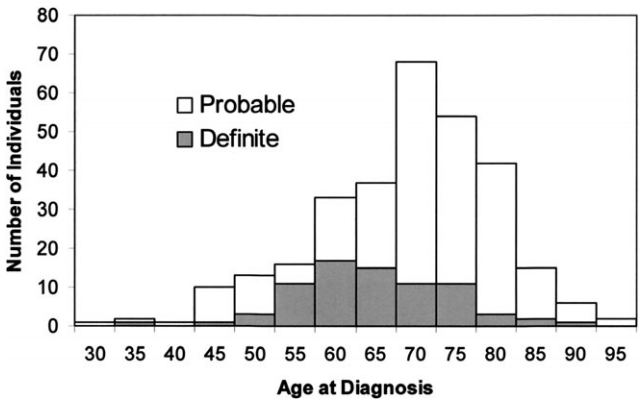

Figure 1. Age of affected subjects at diagnosis. Age at diagnosis is defined as a subject's age at which the first abnormal diagnostic test is reported, prioritized in the following order: (*1*) CXR, (*2*) HRCT, and (*3*) lung biopsy, reported for those with either probable or definite FIP.

TABLE 5. RELATIONSHIP BETWEEN CIGARETTE SMOKING AND FAMILIAL INTERSTITIAL PNEUMONIA

	OR (*95% CI*)	p Value
Univariate analysis		
Unaffected	1.0	
Probable	4.0 (2.8, 5.9)	< 0.00001
Definite	3.7 (1.9, 7.2)	< 0.00001
Probable/definite	4.0 (2.8, 5.6)	< 0.00001
Multivariate analysis*		
Age at examination	1.2 (1.1, 1.2)	0.0004
Sex	1.5 (0.7, 3.3)	0.34
Ever smoking	3.6 (1.3, 9.8)	0.01

Definition of abbreviations: CI = confidence interval; OR = odds ratio.
* In the multivariate analysis, age at examination, sex, and ever cigarette smoking were evaluated as potential risk factors for the development of probable or definite FIP in sibships that included at least one affected family member and one unaffected sibling control with historical smoking data (n = 79 families).

TABLE 6. COMPARISON OF PROBABLE AND DEFINITE FAMILIAL INTERSTITIAL PNEUMONIA

Demographic and Clinical Characteristics	Probable (*n = 231*)	Definite (*n = 78*)
Age, yr, mean ± SD	69.6 ± 11.2	64.5 ± 9.4*
Range (median)	30.3–95.4 (71.2)	35.8–89.4 (63.4)
Male sex, no. (%)	124 (53.7)	48 (61.5)
Age at diagnosis, yr, mean ± SD	68.0 ± 11.1	62.6 ± 9.7*
Range (median)	29.8–94.4 (69.3)	30.9–89.1 (62.4)
Mortality: deaths, no. (%)	102 (44.2)	48 (61.5)†
Age at death, yr, mean ± SD	68.8 ± 10.8	64.7 ± 9.3‡
Range (median)	35.8–87.9 (70.4)	47.3–82.3 (64.2)
Time to death from age at diagnosis, yr, mean ± SD	1.7 ± 2.1	1.0 ± 1.3‡
Cigarette smoking history	n = 188	n = 44
Current smoker, no. (%)	14 (7.4)	4 (9.1)
Former smoker, no. (%)	113 (60.1)	25 (56.8)
Never smoker, no. (%)	61 (32.4)	15 (34.1)
Pack-yr, mean ± SD	16.6 ± 16.2	15.4 ± 15.4
Range (median)	0–62 (15)	0–42 (16)
Mean no. of cigarettes/d	12.0 ± 12.0	13.9 ± 13.0
Range (median)	0–60 (10)	0–40 (13)
Dyspnea		
Dyspnea score, mean ± SD	2.7 ± 1.9	2.8 ± 2.1
Range (median)	0–5 (3)	0–5 (4)
Dyspnea class 0 (none), no. (%)	40 (21.9)	11 (28.2)
Dyspnea class 1–2 (mild), no. (%)	44 (24.0)	6 (15.4)
Dyspnea class 3–4 (moderate), no. (%)	55 (30.1)	7 (17.9)
Dyspnea class 5 (severe), no. (%)	44 (24.0)	15 (38.5)
Vital capacity, %pred: mean ± SD (no.)	69.4 ± 18.7 (98)	63.4 ± 22.5 (32)
Range (median)	28–129 (69.5)	19–97 (63.0)
D_{ICO}, %pred: mean ± SD (no.)	49.8 ± 20.5 (182)	46.2 ± 20.0 (58)
Range (median)	3–132 (50.0)	14–96 (43.5)

Definition of abbreviation: D_{ICO} = carbon monoxide diffusing capacity.
* $p = 0.006$.
† $p < 0.0001$.
‡ $p = 0.02$.

als. The pedigrees include 1,574 parent–offspring pairs, 1,047 sibling pairs, and 785 cousin pairs (Figure E1). As a measure of familial aggregation, we investigated independence in disease status among all sibling pairs in the 111 families (n = 1047) and observed a statistically significant association for risk of disease among siblings (χ^2, 1 df = 75.6; $p < 0.0001$). However, 340 sibling pairs had one or both members with incomplete phenotype data. Even when these were added to the calculations (assuming all were discordant pairs), the results remained highly significant (χ^2, 1 df = 11.8; $p < 0.001$).

Visual inspection of the pedigrees (Figure E1) revealed 20 pedigrees with confirmed vertical transmission involving probable and/or definite cases, including three families with male-to-male transmission, consistent with autosomal dominant inheritance. These pedigrees are consistent with autosomal dominant inheritance; however, autosomal recessive inheritance, more complex modes of inheritance, or heterogeneity in underlying genetic basis between families cannot be fully excluded.

DISCUSSION

Our findings provide convincing support for a genetic basis for IIP. The number (n = 111) of pedigrees presented demonstrates a genetic basis for IIP, and within our families we observed a similar age at diagnosis, a significant risk among siblings, and evidence consistent with an autosomal dominant pattern of inheritance. In addition, we observed an independent association with cigarette smoking, and a substantial proportion of families with phenotypically heterogeneous IIP. These findings suggest that histologically distinct forms of pulmonary fibrosis may have common pathogenic mechanisms and that cigarette smoking may contribute to the development of pulmonary fibrosis in individuals who are genetically prone to this disease.

These findings provide important clues when considering the etiology of pulmonary fibrosis. Whereas the 111 pedigrees present evidence of a genetic basis of IIP, the exposure histories suggest that cigarette smoking is independently associated with the phenotypic expression of this disease. Although the importance of cigarette smoking in the progression of idiopathic pulmonary fibrosis (IPF) remains controversial (35, 36), case-control studies among patients with IPF support our findings in FIP and consistently indicate that cigarette smoking is a risk factor for the development of this disease (37, 38). This suggests that although a certain genotype places an individual at risk of developing pulmonary fibrosis, lung injury substantially contributes to the development of this disease. This "two-hit" hypothesis raises the possibility that an intrinsic inability to adequately repair the injured lung parenchyma may be the fundamental biologic defect that ultimately results in fibrosis and collapse of alveolar units. The hypothesis that a genotypically susceptible individual requires a second "hit" from lung injury to develop disease is supported by the observation that some patients with pulmonary fibrosis related to inherited mutations of surfactant protein C develop respiratory decompensation after respiratory viral infections (23, 39). Alternatively, genes involved in fibroproliferation may be activated by cigarette smoke and possibly other environmental toxins, resulting in abnormal homeostasis of the extracellular matrix. Regardless of the pathogenesis, our findings clearly indicate a delicate balance between injury to the lung and genetic susceptibility to the development of IIP.

Interestingly, a substantial portion of the families with FIP had several radiographic or histologic patterns of IIP, suggesting

that the different histologic types of IIP may be related etiologically and even pathogenically. This suggests that that whereas a susceptibility gene may predispose one to develop FIP, another event (a modifier gene, a medical condition, or a specific exposure) may result in a unique type of IIP. This is the first description of UIP, NSIP, and COP occurring within single families. The familial association of diseases thought to have distinct clinical, radiologic, and pathologic features (IPF/UIP, NSIP, COP, and RB-ILD-like disease) within a pedigree suggests that a susceptibility gene(s) may alter common mechanisms that either enhance the response to injury or diminish the ability to repair the interstitium under conditions of environmental stress. Thus, the pleiotropy observed within our families demonstrates a dynamic relationship between seemingly distinct forms of IIP.

These results also suggest that nearly 8% of self-reported unaffected family members have a preclinical form of FIP. Future studies of FIP will require careful screening of unaffected family members. More importantly, patients with IIP often have a delay in diagnosis, and clinical trials testing novel types of treatment for IPF/UIP suggest the importance of early diagnosis and treatment (40), These individuals may be ideal candidates for early intervention trials. The higher mortality, and younger age at diagnosis or death, observed in patients with definite FIP compared with probable FIP likely represent the greater likelihood of obtaining surgical lung biopsy in younger patients presenting with IIP.

Our study has at least two limitations. In studies aimed at understanding the genetic basis of a disease, there is potential for ascertainment bias due to differential participation of family members. Should younger, female, nonsmoking, unaffected subjects be more likely to participate in the study, then our results would be biased toward finding an association of FIP with older, male smokers. However, we took several measures to minimize ascertainment bias: (*1*) we used a standard, sequential sampling strategy, in which all first-degree relatives and connecting relatives of known affected individuals are approached to participate; (*2*) we conducted direct mailings to local physicians to facilitate obtaining the necessary diagnostic tests; (*3*) we mailed newsletters updating family members on the status of our study, encouraging and stressing the importance of all family members participating in the study; (*4*) we made it easy for family members to participate by including self-addressed, stamped envelopes and toll-free telephone contact numbers; and (*5*) we established regional referral centers. Nevertheless, 25% of family members we contacted chose not to participate in the study, and we do not know the smoking status or demographics of these nonparticipating family members. Protecting the privacy of family members choosing not to participate in the study is a major concern for ethics committees in genetic studies, and we are unable to collect smoking status information directly from these nonparticipating family members. Another limitation of our study is that autopsy or surgical lung biopsy was available from only 74 subjects (23.9%) with probable or definite FIP. In this study, the heterogeneity of FIP subtypes observed with both NSIP and IPF/UIP within a family is based on either surgical lung biopsy or characteristic HRCT scan patterns. In the appropriate clinical setting, the diagnosis of IPF/UIP without surgical biopsy has a sensitivity, specificity, accuracy, and positive predictive value of 85, 43, 68, and 69%, respectively (31). Therefore, some cases diagnosed with probable NSIP by HRCT scan may actually represent IPF/UIP. In addition, the simultaneous occurrence of NSIP and IPF/UIP in a single patient with IIP is well recognized (41). However, we observed a similar distribution of histopathologic subtypes in patients with definite FIP determined by surgical lung biopsy or autopsy compared with our assessment of probable FIP, suggesting heterogeneity detected by HRCT scan truly reflects histopathologic heterogeneity. In addition, families such as VAF44 and DUK66 demonstrate biopsy-proven COP and IPF/UIP or NSIP and IPF/UIP within a family, clearly indicating histopathologic heterogeneity within families with FIP.

In conclusion, our findings support the genetic basis for the development of pulmonary fibrosis. Our findings suggest the possibility that cigarette smoking, or other environmental exposures, may modify the risk of developing pulmonary fibrosis, and the subsequent expression of the disease. Moreover, our findings demonstrate the high risk for this disorder among asymptomatic family members in at least a subset of families, confirming the importance of aggressive surveillance of relatives in families with two or more cases of pulmonary fibrosis.

***Conflict of Interest Statement*:** M.P.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.C.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.E.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. K.K.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.H.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. L.H.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.M.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.P.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.I.S. received $100,000 between 2001 and 2003 for speaking engagements for InterMune, and was a consultant for Centecor in 2001 ($1,500), Immunev in 2001 ($1,500), and Genzyme in 2002 ($2,500), and was on the Advisory Board of InterMune in 2002 ($5,000) and Actelion in 2001–2003 ($5,000). D.A.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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