Respiratory Research

RESEARCH

Open Access

Clinical and genetic features of idiopathic pulmonary fibrosis in a Korean cohort

Chanmi Kim[1], Song Yee Kim[1], A La Woo[1], Ju Hye Shin[1], Mindong Sung[1*] and Moo Suk Park[1*]

Abstract

Background Idiopathic pulmonary fibrosis (IPF) is characterized by substantial genetic heterogeneity across populations, yet genetic features in Asian populations remain underexplored. This study aimed to describe the clinical and genetic landscape of Korean IPF patients and compare findings with reference populations.

Methods The authors analyzed 107 Korean IPF patients from Severance Hospital (2012-2023), including 19 (17.8%) with family history of IPF. Genomic DNA was genotyped using Illumina Multi-Ethnic Genotyping Array. Allele frequencies of 28 IPF-associated SNPs were compared to global and Korean reference populations, and variants within 29 IPF-related genes were analyzed by Fisher's exact tests. Clinical outcomes (survival and longitudinal lung function) were compared between familial and sporadic IPF using Kaplan-Meier and mixed-effects models.

Results Among 107 Korean IPF patients (19 familial, 88 sporadic), three notable findings emerged. First, population-specific SNP differences were observed, with significant depletion of IPF risk variants such as TERT rs2736100 and FAM13A rs2609255 compared with Korean and global reference populations. Second, familial IPF cases showed significantly faster physiological decline, with greater reductions in FVC (−2.36%/year) and DLCO (−4.44%/year), although survival differences were not statistically significant. Third, systematic variant analysis identified 22 potentially pathogenic variants across 7 IPF-related genes, with the highest proportion in epithelial–mesenchymal transition (45.5%) and DNA repair/telomere maintenance (27.3%) pathways, in contrast to the surfactant gene–driven architecture frequently reported in Western cohorts.

Conclusions This descriptive study outlines the clinical and genetic features of Korean IPF patients, highlighting population-specific genomic patterns, more rapid physiological decline in familial cases, and a diverse distribution of potentially pathogenic variants. These findings underscore the importance of incorporating diverse populations into IPF genetic research to refine understanding of disease mechanisms and to inform the development of population-appropriate therapeutic strategies.

Keywords Idiopathic pulmonary fibrosis, Genetics, Family history, Korean population, Population-specific variants, Pulmonary function decline

*Correspondence:
Mindong Sung
mdsung@yuhs.ac
Moo Suk Park
pms70@yuhs.ac
[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease characterized by repetitive epithelial injury and abnormal epithelial-fibroblast interactions leading to fibrosis of the lung parenchyma, resulting in progressive decline in pulmonary function with a poor prognosis [1–3]. Although the exact causes of IPF remain incompletely understood, mounting evidence suggests that both environmental factors and genetic predisposition contribute to disease development and progression [4, 5].

Recent advances in genetic research have identified multiple pathways critical to IPF pathogenesis [6, 7]. These pathways encompass diverse biological processes: DNA repair and telomere maintenance genes (TERT, TERC, RTEL1, PARN, DKC1, OBFC1) regulate cellular aging and tissue repair capacity, with mutations leading to shortened telomeres and premature cell senescence [4]. Immune response and inflammatory signaling genes (TOLLIP, TLR3, CXCL8, IL1RN, MUC5B, MUC5AC, MUC2) control innate immunity and mucosal defense mechanisms [8]. Epithelial-mesenchymal transition and fibrogenesis genes (DSP, TGFB1, CDKN1A, TP53, FOXN3) regulate epithelial cell plasticity and fibrotic remodeling [9]. Additional pathways include cell death and apoptosis regulation (MAPT, ATP11A, DPP9, SPPL2C), surfactant homeostasis and alveolar function (SFTPC, SFTPA2, FAM13A), and signal transduction and growth regulation (AKAP13, LRRC34, IVD) [4].

Importantly, the genetic landscape of IPF demonstrates significant population-specific variation. European and American populations show distinct genetic prevalence patterns compared to East Asian populations [10–12]. For instance, the MUC5B promoter variant (rs35705950), which accounts for nearly 50% of genetic predisposition in European IPF populations, is remarkably rare in East Asian populations [6, 13–15]. These population-specific differences underscore the critical importance of conducting genetic studies within distinct ethnic groups.

Beyond population-level genetic variation, familial clustering of IPF cases provides additional insight into disease genetics and progression patterns. Familial IPF, which is defined by the presence of two or more affected family members, represents approximately 5–20% of IPF cases and offers unique opportunities to study genetic determinants [16]. However, the clinical characteristics and outcomes of familial versus sporadic IPF remain controversial, with studies reporting conflicting findings regarding disease progression patterns [16, 17]. These discrepancies may partly reflect differences in telomere-related genes, which are particularly significant in familial cases [18–21].

Despite growing global research on IPF genetics, studies specifically focused on the Korean population remain limited. This knowledge gap is particularly important given the distinct genetic architecture observed in East Asian populations. Therefore, we conducted a comprehensive descriptive investigation of clinical characteristics and genetic variants in Korean IPF patients. We aimed to characterize the clinical and genetic landscape of IPF in the Korean population, with particular attention to population-specific genomic patterns and subgroup analyses including comparisons between familial and sporadic cases to elucidate differences in genetic characteristics and clinical outcomes.

Materials and methods

Study population and design

We conducted a retrospective cohort study of 107 Korean patients with IPF who received care at Severance Hospital, Seoul, Republic of Korea, between June 2012 and June 2025. All patients were diagnosed with IPF according to the criteria established by the American Thoracic Society/European Respiratory Society [22]. Diagnosis was categorized as having been made based on radiology alone (HRCT-based) or based on histopathology (Surgical lung biopsy-confirmed) according to guideline definitions. In addition, HRCT patterns were stratified into definite and non-definite UIP categories (probable UIP, indeterminate UIP) as recommended by the ATS/ERS guidelines. We comprehensively collected clinical data including family history, baseline pulmonary function, longitudinal pulmonary function progression (forced vital capacity [FVC] and diffusing capacity of the lungs for carbon monoxide [DLCO]), smoking history, lung transplantation status, mortality, comorbidities, and antifibrotic therapy usage. High-resolution computed tomography findings were systematically reviewed according to established guidelines [22].

Although the present analysis was retrospective, information on family history, occupational history, and environmental or occupational exposures was not obtained through unstructured interviews but rather through a systematic, prospective process at the time of each patient's initial outpatient visit or referral for lung transplantation. As part of routine clinical care, all patients underwent evaluation using a dedicated checklist and structured questionnaire, independent of any specific research protocol. This approach ensured standardized documentation across the entire cohort and enhanced the validity and reliability of the collected data.

This study was approved by the Severance Hospital Institutional Review Board (4–2012-0685, 4–2013-0770), and written informed consent was obtained from all participants

Clinical outcome measures

Clinical outcomes included overall survival (time from diagnosis to death from any cause), lung transplant-free

survival (time from diagnosis to lung transplantation), and longitudinal changes in pulmonary function, specifically serial measurements of FVC and DLCO expressed as percentage predicted values adjusted for age, sex, height, and ethnicity.

Genetic profiling and quality control

Genomic DNA was extracted from peripheral blood samples and genotyped using the Illumina Multi-Ethnic Genotyping Array (Illumina, Miami, FL, United States) at the Colorado Anschutz Research Genetics Organization, University of Colorado. Rigorous quality control measures were implemented for both samples and variants, including call rate filtering, Hardy-Weinberg equilibrium testing, and population stratification assessment. Genotype imputation was performed using the Michigan Imputation Server [23] with the East Asian population from the 1000 Genomes Project as the reference panel. Strand harmonization was performed against gnomAD reference data to ensure allelic consistency. QC procedures including sample- and variant-level filtering, imputation, and strand harmonization were applied (see Supplementary Methods for details).

Population-specific common SNP frequency analysis

From this quality-controlled dataset, we extracted and pathway-classified 28 well-characterized IPF-associated single-nucleotide polymorphisms (SNPs) [4, 24, 25] (Supplementary Table 1). Allele frequencies were determined for the entire cohort and compared with multiple reference databases, including gnomAD [26], 1000 Genomes Project [27], Korean Reference Genome Database (KRGDB) [28], TopMed [29], and East Asian-specific databases [26, 27, 29].

Potentially pathogenic variant analysis

We systematically investigated variants within 29 IPF-associated genes across six functional pathways (Supplementary Table 2): DNA repair and telomere maintenance (TERT, TERC, RTEL1, PARN, DKC1, STN1, OBFC1); epithelial-mesenchymal transition and fibrogenesis (DSP, TGFB1, CDKN1A, TP53, FOXN3); immune response and inflammatory signaling (TOLLIP, TLR3, CXCL8, IL1RN, MUC5B, MUC5AC, MUC2); cell death and apoptosis regulation (MAPT, ATP11A, DPP9, SPPL2C); surfactant homeostasis and alveolar function (SFTPC, SFTPA2, FAM13A); and signal transduction and growth regulation (AKAP13, LRRC34, IVD).

Gene coordinates were obtained from Ensembl BioMart (release 110) [29] and expanded by ±10 kb to capture regulatory regions. Variants within these boundaries were extracted using bcftools v1.13 and comprehensively annotated using ANNOVAR (2022-08-02 release) [30]. Annotation included gene context, population allele frequencies from gnomAD East Asian, clinical significance from ClinVar (June 2024 release) [31], and functional predictions from multiple algorithms (SIFT [32], MetaSVM, GERP++, phyloP, phastCons via dbNSFP v4.2c [33–35]).

Variants were classified as potentially pathogenic if they met at least TWO of the following four criteria: (1) MetaSVM score > 0.0 (ACMG/AMP standard threshold for deleterious prediction, as implemented in InterVar), (2) stop-gain mutation (protein-truncating), (3) functional domain location with SIFT damaging prediction, or (4) high evolutionary conservation (GERP++ > 4.0) with SIFT damaging prediction. GERP++ (Genomic Evolutionary Rate Profiling) scores quantify evolutionary constraint at nucleotide positions, with positive scores indicating greater conservation than expected under neutral evolution; scores >4.0 indicate highly conserved positions likely under purifying selection and functionally important. Additional mandatory filtering required GERP++ ≥ 2.0 for all non-stop-gain variants and gnomAD East Asian allele frequency < 0.01 for rare variant selection.

Statistical analysis

Descriptive statistics characterized the study population. Continuous variables were expressed as median (interquartile range) or mean (standard deviation) based on distribution normality. Categorical variables were presented as frequencies and percentages. Between-group comparisons used chi-square or Fisher's exact test (categorical) and Mann-Whitney U or t-test (continuous), as appropriate.

Survival analyses employed Kaplan-Meier curves with log-rank tests for unadjusted comparisons. Multivariable Cox proportional hazards regression assessed familial IPF association with death or transplant, adjusting for age at diagnosis, sex, smoking status, baseline FVC (% predicted, per 10% increase), baseline DLCO (% predicted, per 10% increase), and antifibrotic use.

Longitudinal pulmonary function trajectories were analyzed using linear mixed-effects models (Value ~ Group × Time + Age × Time + Sex × Time + Smoking × Time + Antifibrotic Use × Time + (1|Subject_ID)), where Value represents percentage predicted FVC or DLCO, and Subject_ID accounts for repeated measures. The Group × Time interaction coefficient quantified annual decline rate differences between familial and sporadic IPF. Estimated marginal means and pairwise comparisons assessed between-group differences at each time point.

Subgroup analyses evaluated three predefined stratifications: (1) family history status (familial vs sporadic), (2) diagnostic modality (histologic vs radiologic), and (3) HRCT pattern (definite vs non-definite UIP). These were

applied to clinical outcomes, SNP frequencies, and variant distributions. Diagnostic modality subgroups were further stratified by family history status.

For genetic associations, Fisher's exact test compared allele frequencies between groups, with odds ratios quantifying effect sizes. Carrier status (≥1 alternate allele) was analyzed using 2×2 contingency tables, applying Haldane's 0.5 correction for zero cells. Benjamini-Hochberg false discovery rate (FDR) correction addressed multiple testing, with significance at $P<0.05$ (nominal) and FDR<0.05.

Table 1 Baseline characteristics of Korean IPF patients

Characteristic	Overall (*N* = 107)[a]	Familial (*N* = 19)[a]	Sporadic (*N* = 88)[a]
Age at diagnosis, years	63.0 (58.0, 68.0)	62.0 (55.0, 68.0)	63.5 (59.0, 67.5)
Female	28 (26.2%)	4 (21.1%)	24 (27.3%)
Smoking history			
Current	18 (16.8%)	4 (21.1%)	14 (15.9%)
Former	55 (51.4%)	9 (47.4%)	46 (52.3%)
Never	34 (31.8%)	6 (31.6%)	28 (31.8%)
Pack-years	30.0 (20.0, 48.0)	40.0 (30.0, 45.0)	30.0 (18.4, 49.0)
First-degree family history of IPF	19 (17.8%)	19 (100.0%)	0 (0.0%)
Second-degree family history of IPF	3 (2.8%)	3 (16.7%)	0 (0.0%)
Diagnostic modality			
Histological	72 (67.3%)	9 (47.4%)	63 (71.6%)
Radiological	35 (32.7%)	10 (52.6%)	25 (28.4%)
HRCT pattern			
Definite UIP	62 (57.9%)	13 (68.4%)	49 (55.7%)
Non-definite UIP	45 (42.1%)	6 (31.6%)	39 (44.3%)
FVC, % predicted	82.0 (73.0, 92.0)	82.0 (74.0, 94.0)	82.0 (73.0, 90.0)
DLCO, % predicted	74.0 (60.0, 91.0)	76.0 (60.0, 88.0)	73.0 (60.0, 92.0)
Pirfenidone use	86 (80.4%)	17 (89.5%)	69 (78.4%)
Nintedanib use	3 (2.8%)	1 (5.3%)	2 (2.3%)
COPD	18 (16.8%)	3 (15.8%)	15 (17.0%)
GERD	80 (74.8%)	15 (78.9%)	65 (73.9%)
Hypertension	46 (43.0%)	9 (47.4%)	37 (42.0%)
Dyslipidemia	33 (30.8%)	7 (36.8%)	26 (29.5%)
Cancer history	28 (26.2%)	5 (26.3%)	23 (26.1%)
Lung cancer type			
Adenocarcinoma	6 (66.7%)	0 (0.0%)	6 (85.7%)
Adenocarcinoma or large cell	1 (11.1%)	1 (50.0%)	0 (0.0%)
Small cell carcinoma	1 (11.1%)	0 (0.0%)	1 (14.3%)
Squamous carcinoma	1 (11.1%)	1 (50.0%)	0 (0.0%)
Lung transplant	20 (18.7%)	6 (31.6%)	14 (15.9%)

IPF Idiopathic pulmonary fibrosis, *FVC* Forced vital capacity, *DLCO* Diffusing capacity for carbon monoxide, *COPD* Chronic obstructive pulmonary disease, *GERD* Gastroesophageal reflux disease, *UIP* Usual interstitial pneumonia

[a]Median (IQR) for continuous variables; n (%) for categorical variables

Statistical significance was denoted as *($P<0.05$), **($P<0.01$), ***($P<0.001$). Analyses used R version 4.2.0 with standard statistical and visualization packages.

Results

Entire cohort characteristics

The study cohort comprised 107 Korean patients with IPF, including 19 patients (17.8%) with familial IPF and 88 patients (82.2%) with sporadic IPF. The median age at diagnosis was 63.0 years (IQR: 58.0–68.0), and 79 patients (73.8%) were male. Of the 107 patients, 72 (67.3%) were diagnosed via biopsy, while 35 (32.7%) received a radiological diagnosis. Antifibrotic therapy was administered to most patients, with pirfenidone prescribed in 86 patients (80.4%). Nintedanib was rarely used, with only 3 patients (2.8%) receiving it during the study period.

Gastroesophageal reflux disease (GERD) was the most common comorbidity, present in 80 patients (74.8%). Malignancies were identified in 28 patients (26.2%), with lung cancer diagnosed in 9 cases; adenocarcinoma was the predominant histological subtype (6 cases). Lung transplantation was performed in 20 patients (18.7%), reflecting the role of our institution as an active transplantation center (Table 1).

Subgroup analysis

For the familial versus sporadic subgroup, survival analysis over a median follow-up of 72.0 months revealed no significant survival difference. In multivariable Cox regression adjusting for age, sex, smoking, baseline pulmonary function, and antifibrotic use, familial IPF showed an adjusted hazard ratio of 1.96 for death or transplant (95% CI 0.88–4.35, $P=0.099$). Baseline FVC was independently protective (HR 0.72 per 10% increase, 95% CI 0.55–0.94, $P=0.017$) (Fig. 1). Longitudinal pulmonary function analysis further showed that familial IPF patients experienced faster decline, with an additional −1.6% FVC per year ($P=0.097$) and −3.6% DLCO per year ($P<0.001$) compared with sporadic cases (Fig. 2).

Clinical characteristics showed no significant differences between familial and sporadic groups (Supplementary Table 3 A). Genetic comparisons similarly revealed no significant differences in SNP frequencies (Supplementary Table 3B) or rare variant distributions (Supplementary Table 3 C) after FDR correction, likely reflecting limited statistical power given the small familial cohort ($n=19$). Diagnostic modality and HRCT pattern subgroup analyses also showed no consistent genetic distinctions after multiple testing correction (Supplementary Tables 3D–F).

Population-specific common SNP frequency analysis

Our Korean IPF cohort exhibited distinct allele frequency patterns compared to global and East Asian reference

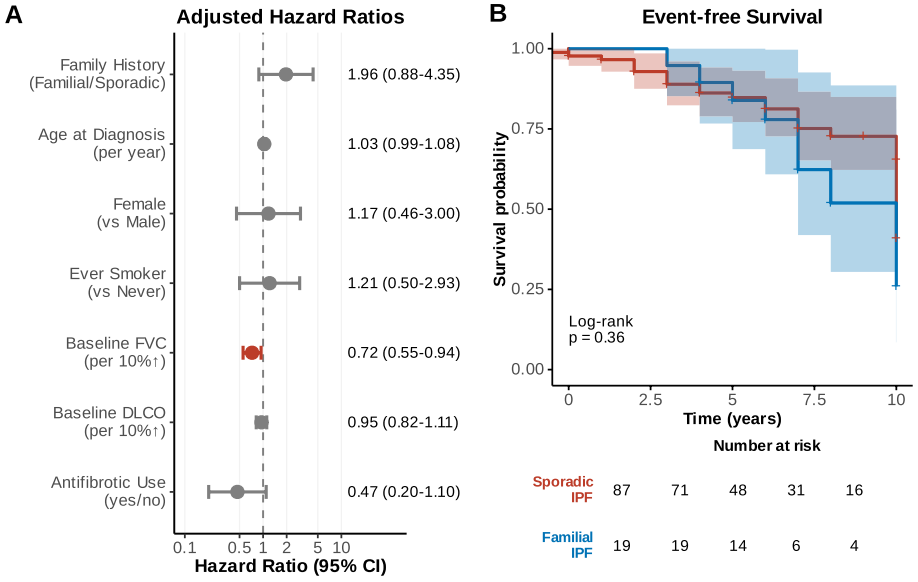

Fig. 1 Survival Outcomes in Korean IPF Cohort. **A** Adjusted hazard ratios from multivariable Cox regression (age, sex, smoking, baseline FVC, baseline DLCO, antifibrotic therapy). **B** Kaplan-Meier curve for death or lung transplantation (*n*=107)

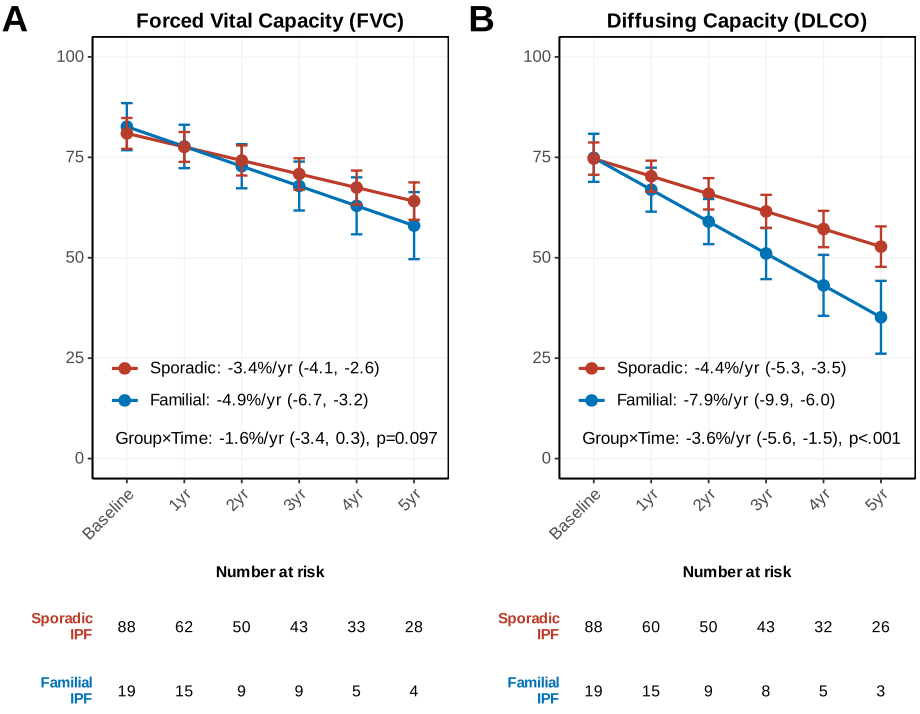

Fig. 2 Pulmonary Function Decline Over Time in Korean IPF. **A** FVC % predicted trajectories over 5 years. **B** DLCO % predicted trajectories over 5 years. Lines show estimated trajectories from mixed-effects models with 95% CI

populations. While most variants showed expected differences from global databases (63 of 90 comparisons significant, 70.0%), several variants demonstrated Korean-specific patterns that diverged even from East Asian and Korean reference populations.

Most notably, MUC5B rs35705950—the strongest known IPF risk variant globally—showed elevated frequency in our Korean IPF cohort (2.8%) compared to the Korean reference (0.3%, q<0.001), suggestive of its pathogenic role across populations. Conversely, TERT rs2736100 and FAM13A rs2609255, both established IPF risk variants, were paradoxically reduced in Korean IPF patients compared to Korean references (27.1% vs. 38.2% and 36.0% vs. 52.7%, respectively; both q<0.001). MAPT rs1981997 was virtually absent in Korean IPF (0.9%) despite frequencies of 12–15% in global populations

(q<0.001), suggesting minimal relevance in Korean IPF pathogenesis (Table 2, Supplementary Table 3 A).

Potentially pathogenic variant landscape

Systematic analysis of 29 IPF-associated genes identified 22 potentially pathogenic variants distributed across 7 genes (Fig. 3). The proportion of variants observed was highest in the epithelial-mesenchymal transition pathway (10/22 variants, 45.5%), followed by DNA repair and telomere maintenance (6/22, 27.3%), immune response pathways (4/22, 18.2%), and cell death/apoptosis regulation (2/22, 9.1%).

At the gene level, DSP exhibited the highest variant count with 8 potentially pathogenic variants (mean GERP++ score: 5.32), followed by TERT with 5 variants (mean GERP++ score: 4.44). DPP9, TGFB1, IL1RN, and MUC5B each harbored 2 variants, while RTEL1 contained 1 variant.

All identified potentially pathogenic variants demonstrated moderate to high conservation (mean GERP++ scores ranging from 3.72 to 5.32) and were completely absent in gnomAD East Asian populations (all allele frequencies = 0%) (Table 3).

Discussion

This study provides a comprehensive description of clinical and genetic features in 107 Korean patients with idiopathic pulmonary fibrosis (IPF), with direct comparisons to reference populations and subgroup analyses. Several noteworthy findings emerged. First, allele frequency comparisons revealed notable differences between the Korean IPF cohort and both Korean and international reference populations, particularly at MAPT, TERT, and FAM13A, suggesting population-specific genetic architectures. Second, longitudinal pulmonary function analyses showed that familial IPF patients experienced faster physiological decline than sporadic cases, although survival outcomes were not significantly different. Third, the diverse distribution of potentially pathogenic variants across multiple functional pathways showed both similarities and differences compared to the surfactant-driven patterns often reported in Western cohorts [36, 37]. Together, these findings highlight the importance of incorporating diverse populations into genetic studies of IPF.

The demographic and clinical profile of our cohort was largely consistent with international studies, characterized by older age, male predominance, and a high proportion of biopsy-confirmed diagnoses. Treatment patterns reflected Korean healthcare policies [38, 39], with pirfenidone widely used and nintedanib rarely prescribed due to insurance restrictions during the study period. Comorbidities followed known IPF associations, including a high prevalence of gastroesophageal reflux disease (GERD) and a substantial burden of lung cancer, predominantly adenocarcinoma. Notably, nearly one in five patients underwent lung transplantation, reflecting both disease severity in our referral population and the active transplantation program at our center, which provides important context for interpreting clinical and genetic outcomes.

Familial IPF patients demonstrated significantly faster decline in FVC and DLCO than sporadic cases, consistent with reports from Western cohorts [40], although no survival differences were detected. Genetic comparisons between familial and sporadic groups revealed no significant differences after correction, likely reflecting limited power due to the small number of familial cases.

Diagnostic heterogeneity is an important concern in IPF research. In our study, genetic profiles were broadly consistent across radiological and histological diagnoses, as well as definite versus non-definite UIP CT patterns. No genetic variants showed significant associations even at the nominal level ($p < 0.05$) when stratified by HRCT pattern. These findings suggest stability of known IPF-associated variants across diagnostic definitions, but larger multi-center studies are required to confirm or refute subtle subgroup effects.

Population-level comparisons underscored distinctive genetic features of Korean IPF patients. MAPT rs1981997 was almost absent, while TERT rs2736100 and FAM13A rs2609255 were consistently reduced compared to Korean and global references. These results support population-specific genomic stratification but should be interpreted cautiously given the absence of healthy Korean controls.

The diverse distribution of potentially pathogenic variants contrasts notably with patterns reported in Western familial IPF [19, 41]. While telomere-related variants were common in both populations, our Korean cohort showed distinctive features: surfactant protein gene variants (SFTPA2, SFTPC, ABCA3) were entirely absent, whereas epithelial–mesenchymal transition variants predominated. These findings should be regarded as hypothesis-generating and suggest that Korean familial IPF may involve distinct or more polygenic mechanisms compared to Western populations [4, 5, 18, 19, 41].

Several limitations should be considered when interpreting these findings. First, the relatively small sample size, particularly the limited number of familial cases (n=19), restricted statistical power and likely contributed to the absence of significant associations after correction. Second, the single-center study design may have introduced referral bias and limits generalizability to the broader Korean population; future multicenter studies will be required for validation. Third, the absence of appropriately matched healthy Korean controls prevented us from distinguishing disease-specific variants

Table 2 Population frequency comparison of selected IPF-associated SNPs

SNP	Gene	Pathway	Ref	Alt	Korean IPF Cohort	gnomAD Global	1000G_Global_Percent	TopMed	gnomAD East Asian	1000G East Asian	Korean Reference	Japanese_Percent	Vietnamese_Percent
rs1278769	ATP11A	Cell death and apoptosis regulation	G	A	31.1	76.2***	77.0***	23.1*	66.4***	72.0***	33.0	30.3	22.0**
rs12610495	DPP9	Cell death and apoptosis regulation	A	G	14.5			23.7**			13.0	12.8	9.9
rs1981997	MAPT	Cell death and apoptosis regulation	G	A	0.9	12.7***	12.0***	15.0***	0.1*	0.2	0.0***	0.0***	
rs17690703	SPPL2C	Cell death and apoptosis regulation	C	T	4.7	16.1***	15.0***	18.0***	7.4	5.0	4.8	4.2	7.9
rs11191865	OBFC1	DNA repair and telomere maintenance	G	A	33.2	44.8**	42.0*	43.2**	34.3	33.0	33.6	33.9	41.6*
rs2736100	TERT	DNA repair and telomere maintenance	A	C	27.1	52.5***	55.0***	47.2***	60.5***	61.0***	38.2**	39.5***	46.7***
rs2076295	DSP	Epithelial-mesenchymal transition and fibrogenesis	G	T	37.9			53.5***			47.1*	50.6***	52.8***
rs4073	CXCL8	Immune response and inflammatory signaling	T	A	35.0			54.7***			36.1		38.4
rs419598	IL1RN	Immune response and inflammatory signaling	T	C	3.7	21.6***	18.0***	20.6***	6.6	8.0*	5.1	5.0	6.9
rs7934606	MUC2	Immune response and inflammatory signaling	C	T	1.4			28.5***				0.3*	
rs35705950	MUC5B	Immune response and inflammatory signaling	G	T	2.8	0.0***			0.0***		0.3***	0.4***	0.5**
rs5743890	TOLLIP	Immune response and inflammatory signaling	T	C	0.0	10.0***	7.0***	9.3***	0.0	0.2		0.0	
rs5743894	TOLLIP	Immune response and inflammatory signaling	T	C	0.0	12.5***	9.0***	11.1***	0.5	0.4	0.2	1.2	3.3**
rs2034650	IVD	Signal transduction and growth regulation	A	G	9.8	47.3***	52.0***	54.8***	80.1***	80.0***	16.2*	15.7*	33.3***
rs2609255	FAM13A	Surfactant homeostasis and alveolar function	G	T	36.0	72.8***	69.0***	73.9***	50.5***	56.0***	52.7***	58.9***	46.7**

Frequencies represent alternative allele frequencies. Significance markers based on FDR-corrected q-values: *** $q < 0.001$, ** $q < 0.01$, * $q < 0.05$

Reference populations: Korean Reference (KRGDB), gnomAD (Genome Aggregation Database), 1000G (1000 Genomes Project), TopMed (Trans-Omics for Precision Medicine)

Primary comparison: Korean IPF vs Korean Reference (6 FDR-significant SNPs). Benjamini-Hochberg FDR correction applied to all 120 Fisher exact tests

Representative SNPs shown. Full Fisher exact test results with FDR q-values available in Supplementary Table 4

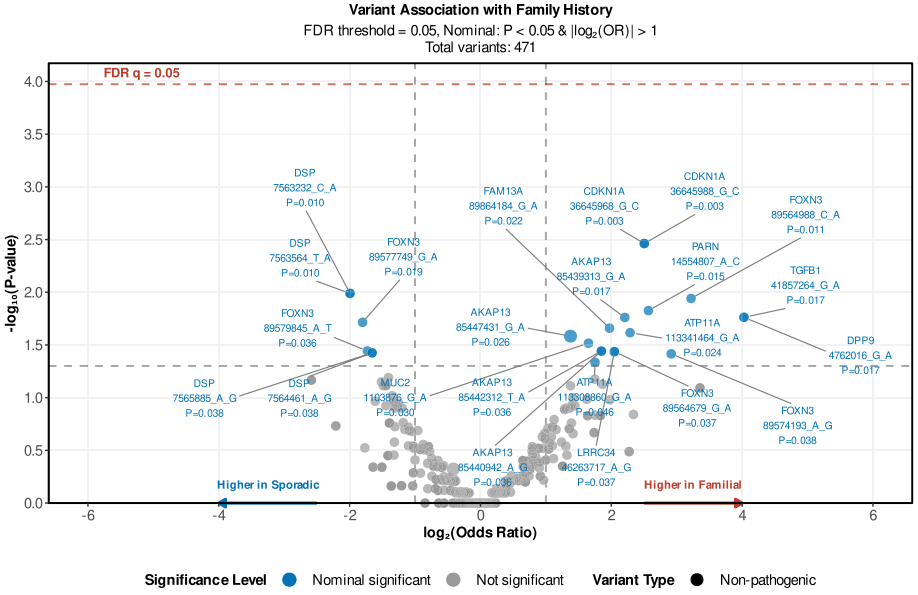

Fig. 3 Genetic Variant Association Analysis with Family History Status. Volcano plot showing association between 471 variants across 29 IPF-associated genes and family history status in Korean IPF cohort (familial *n*=19, sporadic *n*=88). X-axis: $\log_2$(odds ratio); Y-axis: $-\log_{10}$(*P*-value). Dashed lines indicate nominal significance (*P*=0.05, gray), FDR threshold (q=0.25, red), and effect size threshold ($|\log_2(OR)|=1$, vertical). Twenty-three variants showed nominal significance ($P<0.05$ and $|\log_2(OR)|>1$) in genes CDKN1A, DSP, FOXN3, PARN, DPP9, and TGFB1. However, no variants survived FDR correction (q<0.05), reflecting limited statistical power from small familial subgroup size. These represent hypothesis-generating findings requiring validation in larger cohorts

Table 3 Potentially pathogenic variant distribution across IPF-associated pathways

Pathway	Gene	Total	Stop	Meta SVM	Cons.	Domain	Mean MetaSVM	Mean GERP++
Epithelial-Mesenchymal Transition	DSP	8	0	3	10	7	−0.146	5.320
	TGFB1	2	0	2			0.629	4.230
Cell Death & Apoptosis Regulation	DPP9	2	0	2	0	2	0.617	3.720
DNA Repair & Telomere Maintenance	TERT	5	0	4	5	4	0.609	4.440
	RTEL1	1	0	1			1.108	4.350
Immune Response & Inflammation	IL1RN	2	0	2	4	1	0.618	4.500
	MUC5B	2	0	1			0.044	4.580

Variants classified as potentially pathogenic using ACMG/AMP-standard MetaSVM threshold (>0.0, per InterVar; Li & Wang, Am J Hum Genet 2017)

Total: 22 variants across 7 genes in 4 pathways. Confidence levels (High/Moderate/Low) provided in Supplementary Table 5

Classification criteria (≥2 REQUIRED): Stop (stop-gain, 4 pts), MetaSVM (>0, 1 pt), Cons. (GERP++>4.0 + SIFT damaging, 1 pt), Domain (functional domain + SIFT damaging, 2 pts)

Additional filters: GERP++ ≥ 2.0 (except stop-gain), gnomAD EAS AF < 0.01. Criteria columns show pathway-level counts

Top genes: DSP (8), TERT (5), DPP9/IL1RN/MUC5B/TGFB1 (2 each). Detailed variant information in Supplementary Table 5

from population-specific polymorphisms. Fourth, variant pathogenicity was inferred primarily from in silico prediction tools, as publicly available databases such as ClinVar lacked annotations for the variants identified in our cohort. This absence reflects the underrepresentation of Asian populations in variant databases and limits our ability to assess clinical significance using curated evidence. Finally, functional validation will be necessary to confirm the biological impact of the candidate variants identified.

Conclusion

In this Korean IPF cohort, we observed population-specific genetic patterns, a tendency for faster functional decline in familial cases, and a diverse distribution of potentially pathogenic variants, with the highest proportion in epithelial–mesenchymal transition and DNA repair/telomere maintenance pathways. These findings, while limited by sample size, suggest that IPF in Korean patients may involve distinct pathogenic mechanisms and underscore the importance of population-specific research to advance understanding of disease pathogenesis.

Abbreviations

IPF	Idiopathic pulmonary fibrosis
FVC	Forced vital capacity
DLCO	Diffusing capacity of the lung for carbon monoxide
SNP	Single nucleotide polymorphism
DNA	Deoxyribonucleic acid
HRCT	High-resolution computed tomography
UIP	Usual interstitial pneumonia
GERD	Gastroesophageal reflux disease
OR	Odds ratio
CI	Confidence interval
FDR	False discovery rate
GERP++	Genomic Evolutionary Rate Profiling

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-026-03504-w.

Supplementary Material 1.

Acknowledgments

The authors thank all patients and their families for participating in this study. The authors specially thank to Dr. Anna and Dr. David for genetic analysis of Korean IPF patients.

Authors' contributions

C. Kim, M. Sung, and M. Park are the guarantors of the manuscript. All authors reviewed and edited this manuscript as appropriate. C. Kim, M. Sung and M. Park conceived and designed the study. C. Kim, M. Sung and M. Park worked on the methods. S. Kim, A. Woo, J. Shin and M. Park contributed to the investigation and resources. C. Kim and M. Sung wrote the original draft. M. Sung, M. Park supervised the study, contributed to data analysis and manuscript review, and served as corresponding authors. All authors reviewed and approved the final manuscript.

Funding

The authors have reported to ***Respiratory research*** that no funding was received for this study

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request, subject to appropriate ethics approval and data sharing agreements.

Declarations

Ethics approval and consent to participate

This study was approved by the Severance Hospital Institutional Review Board (IRB#: 4-2012-0685, 4-2013-0770). Written informed consent was obtained from all participants prior to their inclusion in the study.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests.

Received: 15 July 2025 / Accepted: 6 January 2026
Published online: 30 January 2026

References

1. Costabel U, Crestani B, Wells AU. Introduction. In: Idiopathic Pulmonary Fibrosis. European Respiratory Society; 2025. p. x–xi. https://doi.org/10.1183/2312508X.10003016.
2. Craig VJ, Zhang L, Hagood JS, Owen CA. Matrix metalloproteinases as therapeutic targets for idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol. 2015;53(5):585–600. https://doi.org/10.1165/rcmb.2015-0020TR.
3. Mei Q, Liu Z, Zuo H, Yang Z, Qu J. Idiopathic pulmonary fibrosis: an update on pathogenesis. Front Pharmacol. 2022;12:797292. https://doi.org/10.3389/fphar.2021.797292.
4. Kropski JA, Blackwell TS, Loyd JE. The genetic basis of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(6):1717–27. https://doi.org/10.1183/09031936.00163814.
5. Abbasi A, Chen C, Gandhi CK, Wu R, Pardo A, Selman M, et al. Single Nucleotide Polymorphisms (SNP) and SNP-SNP Interactions of the Surfactant Protein Genes Are Associated With Idiopathic Pulmonary Fibrosis in a Mexican Study Group; Comparison With Hypersensitivity Pneumonitis. Front Immunol. 2022;Volume 13-2022. Available from: https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.842745.
6. Adegunsoye A, Kropski JA, Behr J, Blackwell TS, Corte TJ, Cottin V, et al. Genetics and genomics of pulmonary fibrosis: charting the molecular landscape and shaping precision medicine. Am J Respir Crit Care Med. 2024;210(4):401–23. https://doi.org/10.1164/rccm.202401-0238SO.
7. Mahalanobish S, Ghosh S, Sil PC. Genetic underpinnings of pulmonary fibrosis: an overview. Cardiovasc Hematol Agents Med Chem. 2024;22(3):367–74. https://doi.org/10.2174/0118715257261006231207113809.
8. Partanen JJ, Häppölä P, Zhou W, Lehisto AA, Ainola M, Sutinen E, et al. Leveraging global multi-ancestry meta-analysis in the study of idiopathic pulmonary fibrosis genetics. Cell Genom. 2022;2(10):100181. https://doi.org/10.1016/j.xgen.2022.100181.
9. Michalski JE, Schwartz DA. Genetic Risk Factors for Idiopathic Pulmonary Fibrosis: Insights into Immunopathogenesis. J Inflamm Res. 2020;13:1305–18. https://doi.org/10.2147/JIR.S280958.
10. Kishore A, Žižková V, Kocourková L, Petrkova J, Bouros E, Nunes H, et al. Association study for 26 candidate loci in idiopathic pulmonary fibrosis patients from four European populations. Front Immunol. 2016;7:274. https://doi.org/10.3389/fimmu.2016.00274.
11. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet. 2013;45(6):613–20. https://doi.org/10.1038/ng.2609.
12. Hong D, Dai D, Liu J, Zhang C, Jin T, Shi Y, et al. Clinical and genetic spectrum of interstitial lung disease in Chinese children associated with surfactant protein C mutations. Ital J Pediatr. 2019;45(1):117. https://doi.org/10.1186/s13052-019-0710-2.
13. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, et al. A common MUC5B promoter polymorphism and pulmonary fibrosis. N Engl J Med. 2011;364:1503–12. https://doi.org/10.1056/NEJMoa1013660.
14. Zhang Y, Noth I, Garcia JGN, Kaminski N. A variant in the promoter of MUC5B and idiopathic pulmonary fibrosis. N Engl J Med. 2011;364:1576–7. https://doi.org/10.1056/NEJMc1013504.
15. Yang IV, Fingerlin TE, Evans CM, Schwarz MI, Schwartz DA. MUC5B and Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc. 2015;12 Suppl 2(Suppl 2):S193-199. https://doi.org/10.1513/AnnalsATS.201503-110AW.
16. Krauss E, Gehrken G, Drakopanagiotakis F, Tello S, Dartsch RC, Maurer O, et al. Clinical characteristics of patients with familial idiopathic pulmonary fibrosis (f-IPF). BMC Pulm Med. 2019;19(1):130. https://doi.org/10.1186/s12890-019-0895-6.
17. Lee HL, Ryu JH, Wittmer MH, Hartman TE, Lymp JF, Tazelaar HD, et al. Familial idiopathic pulmonary fibrosis: clinical features and outcome. Chest. 2005;127(6):2034–41. https://doi.org/10.1378/chest.127.6.2034.
18. Stuart BD, Choi J, Zaidi S, Xing C, Holohan B, Chen R, et al. Exome sequencing links mutations in PARN and RTEL1 with familial pulmonary fibrosis and telomere shortening. Nat Genet. 2015;47(5):512–7. https://doi.org/10.1038/ng.3278.
19. Zhang K, Xu L, Cong YS. Telomere dysfunction in idiopathic pulmonary fibrosis. Front Med. 2021;8:739810. https://doi.org/10.3389/fmed.2021.739810.
20. Kropski JA, Loyd JE. Telomeres revisited: RTEL1 variants in pulmonary fibrosis. Eur Respir J. 2015;46(2):312–4. https://doi.org/10.1183/13993003.00710-2015.
21. Neely ML, Hellkamp AS, Bender S, Todd JL, Liesching T, Luckhardt TR, et al. Lung function trajectories in patients with idiopathic pulmonary fibrosis. Respir Res. 2023;24(1):209. https://doi.org/10.1186/s12931-023-02503-5.
22. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44-68. https://doi.org/10.1164/rccm.201807-1255ST.

23. Das S, Forer L, Schönherr S, Sidore C, Locke AE, Kwong A, et al. Next-generation genotype imputation service and methods. Nat Genet. 2016;48(10):1284–7. https://doi.org/10.1038/ng.3656.
24. Kaur A, Mathai SK, Schwartz DA. Genetics in Idiopathic Pulmonary Fibrosis Pathogenesis, Prognosis, and Treatment. Front Med. 2017;4. Available from: https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2017.00154/full. https://doi.org/10.3389/fmed.2017.00154. Cited 2025 Dec 15.
25. Peljto AL, Selman M, Kim DS, Murphy E, Tucker L, Pardo A, et al. The MUC5B promoter polymorphism is associated with idiopathic pulmonary fibrosis in a Mexican cohort but is rare among Asian ancestries. Chest. 2015;147(2):460–4. https://doi.org/10.1378/chest.14-0867.
26. Chen S, Francioli LC, Goodrich JK, Collins RL, Kanai M, Wang Q, et al. A genomic mutational constraint map using variation in 76,156 human genomes. Nature. 2024;625(7993):92–100. https://doi.org/10.1038/s41586-023-06045-0.
27. Auton A, Abecasis GR, Altshuler DM, Durbin RM, Abecasis GR, Bentley DR, et al. A global reference for human genetic variation. Nature. 2015;526(7571):68–74. https://doi.org/10.1038/nature15393.
28. Jung KS, Hong KW, Jo HY, Choi J, Ban HJ, Cho SB, et al. KRGDB: the large-scale variant database of 1722 Koreans based on whole genome sequencing. Database Oxford. 2020;2020:baaa030. https://doi.org/10.1093/database/baaa030.
29. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed program. Nature. 2021;590(7845):290–9. https://doi.org/10.1038/s41586-021-03205-y.
30. Wang K, Li M, Hakonarson H. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. Nucleic Acids Res. 2010;38(16):e164. https://doi.org/10.1093/nar/gkq603.
31. Landrum MJ, Lee JM, Benson M, Brown GR, Chao C, Chitipiralla S, et al. ClinVar: improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46(D1):D1062-7. https://doi.org/10.1093/nar/gkx1153.
32. Ng PC, Henikoff S. SIFT: Predicting amino acid changes that affect protein function. Nucleic Acids Res. 2003;31(13):3812–4. https://doi.org/10.1093/nar/gkg509.
33. Liu X, Jian X, Boerwinkle E. dbNSFP: a lightweight database of human nonsynonymous SNPs and their functional predictions. Hum Mutat. 2011;32(8):894–9. https://doi.org/10.1002/humu.21517.
34. Liu X, Li C, Mou C, Dong Y, Tu Y. dbNSFP v4: a comprehensive database of transcript-specific functional predictions and annotations for human nonsynonymous and splice-site SNVs. Genome Med. 2020;12(1):103. https://doi.org/10.1186/s13073-020-00803-9.
35. Dong C, Wei P, Jian X, Gibbs R, Boerwinkle E, Wang K, et al. Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies. Hum Mol Genet. 2015;24(8):2125–37. https://doi.org/10.1093/hmg/ddu733.
36. Fernandez BA, Fox G, Bhatia R, Sala E, Noble B, Denic N, et al. A Newfoundland cohort of familial and sporadic idiopathic pulmonary fibrosis patients: clinical and genetic features. Respir Res. 2012;13(1):64. https://doi.org/10.1186/1465-9921-13-64.
37. Baratella E, Ruaro B, Giudici F, Wade B, Santagiuliana M, Salton F, et al. Evaluation of correlations between genetic variants and high-resolution computed tomography patterns in idiopathic pulmonary fibrosis. Diagnostics. 2021;11(23):762. https://doi.org/10.3390/diagnostics11050762.
38. Jegal Y, Park JS, Kim SY, Yoo H, Jeong SH, Song JW, et al. Clinical Features, Diagnosis, Management, and Outcomes of Idiopathic Pulmonary Fibrosis in Korea: Analysis of the Korea IPF Cohort (KICO) Registry. Tuberc Respir Dis. 2021;85(2):185–94. https://doi.org/10.4046/trd.2021.0123.
39. Chua F, Nyanti LE, Tan SH, Aflah SSS, Kho SS, Chai GT, et al. Pharmacoeconomic inequalities in access to antifibrotic treatment for interstitial lung disease in the Asia-Pacific region. Tuberc Respir Dis. 2025;88(4):673–86. https://doi.org/10.4046/trd.2025.0056.
40. Krauss E, Gehrken G, Drakopanagiotakis F, Tello S, Dartsch RC, Maurer O, et al. Clinical characteristics of patients with familial idiopathic pulmonary fibrosis (f-IPF). BMC Pulm Med. 2019;19(1):130. https://doi.org/10.1186/s12890-019-0895-6.
41. Borie R, Kannengiesser C, Antoniou K, Bonella F, Crestani B, Fabre A, et al. European Respiratory Society statement on familial pulmonary fibrosis. Eur Respir J. 2023;61(3):2201383. https://doi.org/10.1183/13993003.01383-2022.

Publisher's Note