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Telomere dysfunction and mucociliary impairment drive idiopathic pulmonary fibrosis susceptibility: insights from a Sardinian whole-exome study

Stefano Mocci,[1,2] Roberto Littera,[3] Silvia Deidda,[4] Federica Cannas,[1,2] Chiara Cocco,[1] Michela Lorrai,[1] Caterina Mereu,[1] Michela Murgia,[1] Giulia Nutile,[1] Francesco Lai,[5] Celeste Sanna,[1] Laura Serventi,[1] Gaia Tosone,[1] Elena Zedda,[1] Erika Giuressi,[3] Sara Lai,[3] Andrea Perra,[6] Matteo Floris ,[1,3,7] Sabrina Giglio[2,3,8]

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SM and RL contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Matteo Floris; matteo.floris@gmail.com

ABSTRACT

Background Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease in which both environmental exposures and genetic predisposition contribute to disease susceptibility. Studying the burden of rare variants in a genetically homogeneous founder population may help identify disease-associated alleles that are difficult to detect in more heterogeneous populations.

Methods Whole exome sequencing was performed on 123 patients with IPF and 1110 unrelated controls from Sardinia (Italy). Variant prioritisations were conducted according to the American College of Medical Genetics (ACMG) guidelines. In parallel, gene burden of rare predicted loss-of-function variants was assessed using the Cohort Allelic Sums Test (CAST) algorithm to identify genes significantly enriched in IPF cases compared with controls.

Results Pathogenic or likely pathogenic variants in known telomere-related genes were identified in 11.4% of patients. These variants were associated with younger age at diagnosis and a higher prevalence among never-smokers. CAST analysis identified a significant enrichment of loss-of-function variants in 82 genes, including *MUC5B* (OR=443.1, false discovery rate=3.7E−05), functionally related to cilium organisation and motility, with a significant overrepresentation of dynein-related genes.

Conclusions This study supports the contribution of telomere-related variants to IPF susceptibility and suggests a possible role for rare variants affecting mucociliary pathways. Together, these findings broaden the current understanding of IPF biology in this cohort. The distinctive genetic background of the Sardinian population may have facilitated the identification of rare or population-specific variants, underscoring the potential value of founder populations in complex disease genetics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Genetic susceptibility plays a key role in idiopathic pulmonary fibrosis (IPF), particularly through rare pathogenic variants in telomere maintenance genes, which contributes to epithelial cell senescence and impaired alveolar repair.

WHAT THIS STUDY ADDS

⇒ This study confirms the presence of rare pathogenic variants in telomere-related genes and provides, for the first time, novel evidence of a significant enrichment of rare loss-of-function variants in genes involved in cilium organisation and motility, particularly dynein-associated genes (eg, DNAH5, DNAH6, HYDIN).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study broadens the current understanding of IPF's pathogenic mechanisms and supports inclusion of both telomere-related and cilia-related genes in future risk prediction models, emphasising the need for more comprehensive genetic testing in clinical practice.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease (ILD) characterised by excessive fibrosis and structural remodelling of the lung parenchyma.[1] Clinical symptoms mainly include chronic cough and exertional dyspnoea, along with restrictive patterns on pulmonary function tests and impaired gas exchange.[2]

Epidemiological estimates based on broad diagnostic criteria suggest an incidence ranging from 2 to 30 cases per 100 000 person-years and a prevalence between 10 and 60 cases per 100 000 individuals, with approximately 3 million cases globally.[3–5] Most studies indicate a slight male predominance.[6]

IPF is a heterogeneous disease that can occur sporadically or, in approximately 2%–20% of cases, within families.[7 8]

The exact cause of IPF remains unknown; however, it is generally accepted that repeated alveolar epithelial injury, followed

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by aberrant tissue repair, plays a central role in disease pathogenesis.[9] Unlike other ILDs, IPF is primarily driven by epithelial dysfunction rather than chronic inflammation.[10] Dysfunctional alveolar epithelial cells promote fibroblasts' migration, proliferation and differentiation into myofibroblasts, leading to excessive extracellular matrix deposition and progressive fibrosis.[11]

It is also now well understood that genetic susceptibility and environmental risk factors have a major contribution to the risk of developing IPF.[6 11–13] Both rare and common genetic variants contribute to disease susceptibility.[14] One of the strongest known genetic risk factors for IPF is a gain-of-function mucin 5B (*MUC5B*) promoter SNP (*rs35705950*), which leads to increased *MUC5B* expression, particularly in the distal airways and honeycomb cysts.[15 16] Studies in mice have shown that both *Muc5b* deficiency and overexpression result in impaired mucociliary clearance (MCC).[17]

Moreover, rare pathogenic variants in telomere-maintenance genes have been associated with IPF and telomere shortening[14 18 19] and have been found in ~15%–20% of IPF families.[14 18–22] Telomere shortening has been observed in about one-third of patients with IPF without identifiable mutations, implying other genetic or environmental contributions.[13 23 24]

Also rare heterozygous variants in surfactant protein genes (eg, *SFTPC, SFTPA2*) have been associated with familial interstitial pneumonia, accounting for 1%–2% of cases.[25–32]

Given the recognised role of genetic predisposition in IPF, this study explored the genetic determinants of IPF susceptibility in a well-characterised Sardinian patient cohort. The relatively homogeneous genetic background of Sardinians may enhance the detection of rare or locally enriched variants that are more difficult to identify in genetically diverse groups.[28]

MATERIALS AND METHODS

Patient recruitment

A total of 170 patients with IPF were recruited over a 36-month period, from January 2022 to January 2025, at the Department of Pulmonology, Binaghi Hospital (ASL Cagliari, Italy) (figure 1). The diagnosis of IPF and progressive pulmonary fibrosis was made according to the international guidelines.[29] Both sporadic and familial IPF cases were included in the study.

Key clinical and demographic variables and longitudinal respiratory function measures were collected, and after applying inclusion/exclusion criteria the final cohort comprised 123 patients with IPF compared with 1110 Sardinian controls, with full details provided in the online supplemental methods.

Patient and public involvement

Patient and public involvement in this research was primarily through the recruitment process and informed consent procedures. Patients were recruited from January 2022 to January 2025 at the Department of Pulmonology, Binaghi Hospital (ASL Cagliari, Italy). All patients and controls provided written informed consent in accordance with institutional and national ethical standards, and the study protocol was approved by the Ethics Committee of the University Hospital of Cagliari. Informed consent documents are securely stored in hospital records and are part of each patient's medical file.

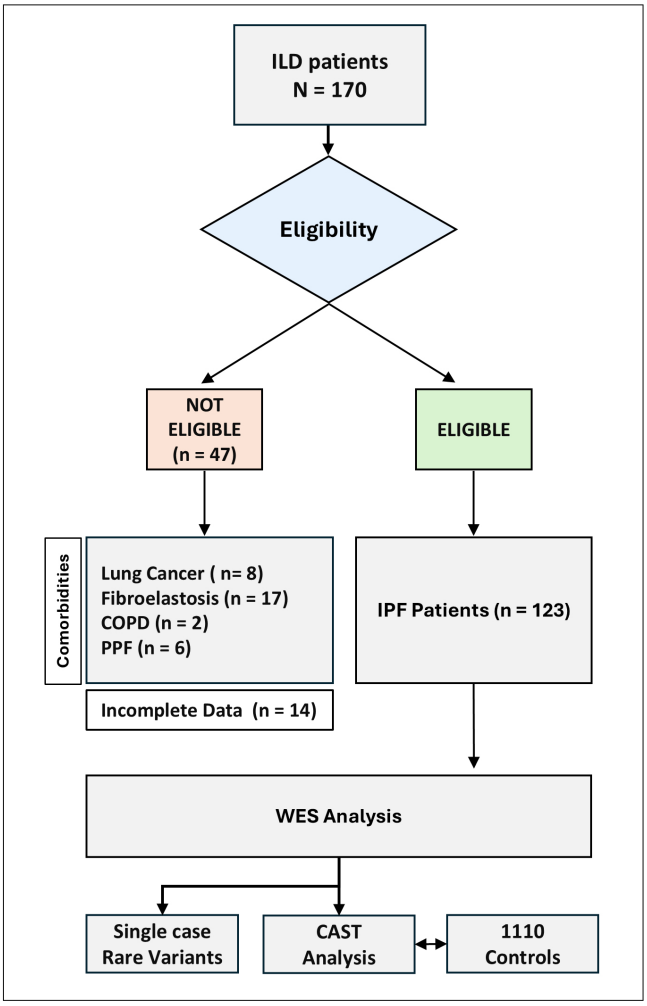

Figure 1 Study cohort selection and WES workflow. Flowchart illustrating the selection of the study cohort and the downstream genetic analysis. Out of 170 patients with ILD, 29 were excluded due to alternative diagnoses (lung cancer, fibroelastosis, COPD, PPF), fibroelastosis or incomplete data. A total of 123 patients with IPF were included and underwent WES. Identified variants were then analysed as single-case rare variants and through CAST burden analysis, with comparison to 1110 healthy controls. CAST, Cohort Allelic Sums Test; COPD, Chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PPF, progressive pulmonary fibrosis; WES, whole-exome sequencing.

Disease-causing variants for gene burden testing

Gene-based burden testing was performed using the Cohort Allelic Sums Test (CAST) statistic on rare

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predicted LoF variants, followed by Fisher's exact test and Firth's logistic regression (adjusted for relevant covariates), with multiple testing correction applied; pathway and visualisation analyses were conducted using GO terms and standard R packages.

Full methodological details are provided in the online supplemental methods.

RESULTS

Clinical characteristics of the cohort

The final study cohort included 123 patients. Mean age at diagnosis was 70.0±8.5 years and 99 (80.5%) patients were male. A family history of IPF was reported in 22 (17.9%) patients, whereas no family history was reported in the remaining 101 patients. Regarding smoking history, 83 (67.5%) patients were former smokers, 31 (25.2%) had never smoked and 9 (7.3%) were current smokers. At baseline, mean forced vital capacity (FVC) was 2648.7±809.9 mL, mean FVC% predicted was 84.2±60.1 and mean DLCO% predicted (Diffusing Capacity of the Lungs for Carbon Monoxide) was 65.0±19.7. Most patients received antifibrotic treatment, with nintedanib being the most frequently used drug (64/123, 52.0%), followed by pirfenidone (19/123, 15.4%), while 26 (21.1%) patients switched treatment during follow-up and 14 (11.4%) received no antifibrotic therapy. Detailed longitudinal clinical data are reported in online supplemental table S2.

WES results

Whole-exome sequencing (WES) identified 14 (14/123, 11.4%) patients carrying a pathogenic or likely pathogenic variant in the filtered genes (online supplemental table 1). In addition, variants of uncertain significance (VUS) were identified in 8 (8/123, 6.5%) patients; these variants were rare and uniquely found in these individuals.

Most pathogenic variants were in genes involved in the telomere maintenance pathway: six patients carried a variant in *TERT*, three in *CTC1*, two in *PARN* and three in *RTEL1*. Among these, two familial clusters were identified, one including two brothers (*CTC1* c.2944delG; p.Val982fs) and another comprising three sisters (*TERT* c.316G>A; p.Gly106Arg) (table 1; Group family AA and AB). Family history of IPF was reported in 7 of the 14 patients carrying a pathogenic or likely pathogenic telomere-pathway variant (50.0%), compared with 13 of 101 variant-negative patients (12.9%) and 2 of 8 patients carrying a VUS (25.0%) (p=0.003); online supplemental table S2). Notably, five individuals (Family AA and AB) of these seven familial cases belonged to the two multiplex families described above, whereas the remaining two were apparently unrelated carriers who reported an affected father or aunt.

Extrapulmonary features were documented in 4 of the 14 carriers of pathogenic or likely pathogenic variants. Premature greying of hair was observed in three patients, liver cirrhosis in one, osteoporosis in one and myelodysplastic syndrome in 1 (table 1).

Furthermore, VUS were identified in *CTC1* (n=2 patients), *PARN* (n=3), *TERT* (n=2), and *RTEL1* (n=1) (table 1). All identified variants were either missense mutations or small deletions.

Notably, 12 variants identified in this cohort were not present in gnomAD, suggesting their rarity in the general population. Moreover, a total of 13 variants were not reported in ClinVar, and in some cases, discrepancies between ClinVar and Franklin classifications were observed.

As reported in online supplemental table S2, the mean age at diagnosis was 70.0±8.5 years, and 99 (80.5%) patients were male. A total of 67.5% of patients (n=83) were former smokers and 9 (7.3%) patients were current smokers. At baseline, the Forced Vital Capacity predicted (FVCp%) was 84.2±60.1, decreasing to 71.7±17.3 after 36 months.

Patients carrying pathogenic or likely pathogenic telomere-pathway variants were more frequently diagnosed before 65 years of age than variant-negative patients (46.2% vs 13.7%, p=0.008). An even stronger enrichment was observed for very early disease onset, defined as diagnosis before 50 years of age (23.1% vs 0.0%, p=0.001). In addition, a family history of IPF was more frequent in the pathogenic/likely pathogenic group than in the negative and VUS groups (50.0% vs 12.9% and 25.0%, respectively; p=0.003) (online supplemental table S4). No significant differences were observed in sex distribution (p=0.534), whereas smoking history differed across groups (p=0.044), with carriers of pathogenic or likely pathogenic telomere-pathway variants being more frequently never-smokers than variant-negative patients (53.8% vs 20.6%).

Finally, as shown in online supplemental table 3, clinical features suggestive of telomere biology disorders were overall uncommon, although premature greying of hair was restricted to the pathogenic/likely pathogenic telomere-pathway group, while liver cirrhosis and haematological abnormalities were rare and variably distributed across groups.

CAST analysis

The CAST burden analysis compared the gene-level burden of rare predicted loss-of-function (LoF) variants between cases and controls. For this analysis, a subset of 99 patients with IPF was selected from the initial cohort of 123, excluding individuals with familial relatedness and/or non-Sardinian ancestry, to reduce potential confounding from shared genetic background or population stratification. These 99 cases were compared with 1110 unrelated population controls without documented pulmonary disease.

For each test, the CAST value was used as a covariate in Firth's logistic regression, adjusting for sex and age and family history, which identified a total of 82 statistically significant genes (figure 2). However, after panel-based

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Table 1 Pathogenic Variants and VUS in genes involved in the telomere maintenance pathway

Individual ID	Gene	Variant	gnomAD ENF	ClinVar Accession Number	ClinVar classification	Franklin (Geenox)	Family group	Phenotype	Family history of ILD
45	*CTC1 (NM_025099.6)*	c.(2944delG);(=) p.(Val982fs);(=)	–	–	-	LP	AB		Sister
73	*CTC1 (NM_025099.6)*	c.(2944delG);(=) p.(Val982fs);(=)	–	–	-	LP	AB		Brother
143	*CTC1 (NM_025099.6)*	c.(2199_2201del);(=); p.(Phe733del);(=)	–	VCV003270021.1	VUS	LP		Liver cirrhosis, premature greying of hair	
12	*PARN (NM_002582.4)*	c.(739G>T);(=) p.(Glu247*);(=)	–	–	-	LP			
133	*PARN (NM_002582.4)*	c.(1671–2A>G);(=) p.(?);(=)	–	–	-	LP			
25	*RTEL1 (NM_001283009.2)*	c.(1675T>A);(=) p.(Phe559Ile); [=}	0.000005932	VCV000473909.14	VUS	LP			
34	*RTEL1 (NM_001283009.2)*	c.(3776_3779del);(=) p.(Ala1259*);(=),	0.0000008	VCV001452682.6	P	LP		Premature greying of hair	
76	*RTEL1 (NM_001283009.2)*	c.(2956C>T);(=) p.(R986*);(=)	0.00004454	VCV000065417.81	P	P			
5	*TERT (NM_198253.3)*	c.(316G>A);(=) p.(Gly106Arg);(=)	–	–	-	LP	AA	Osteoporosis	Mother, sisters
16	*TERT (NM_198253.3)*	c.(316G>A);(=) p.(Gly106Arg);(=)	–	–	-	LP	AA		Mother, sisters
18	*TERT (NM_198253.3)*	c.(316G>A);(=) p.(Gly106Arg);(=)	–	–	-	LP	AA		Mother, sisters
46	*TERT (NM_198253.3)*	c.(–124C>T)(=)p.(?);(=)	0.0001096	VCV001299388.19	LP	LP	AC		Aunt
69	*TERT (NM_198253.3)*	c.(1168C>T);(=) p.(Arg390Trp);(=)	–	VCV001055658.7	VUS	LP			
84	*TERT (NM_198253.3)*	c.(2921T>G);(=) p.(Leu974Arg);(=)	–	–	-	LP	AE	Myelodysplastic syndrome, premature greying of hair	Father
85	*CTC1 (NM_025099.6)*	c.(1607C>T);(=) p.(P536L);(=)	0.00000171	–	VUS	VUS	AF		Mother
146	*CTC1 (NM_025099.6)*	c.(515A>G);(=) p.(N172S);(=)	0.00001271	–	VUS	VUS			

Continued

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Table 1 Continued

Individual ID	Gene	Variant	gnomAD ENF	ClinVar Accession Number	ClinVar classification	Franklin (Geenox)	Family group	Phenotype	Family history of ILD
52	*PARN (NM_002582.4)*	c.(34C>T);(=) p.(L12F);(=)	0.000005938	VCV000663050.7	VUS	VUS			
99	*PARN (NM_002582.4)*	c.(1167C>G);(=) p.(Cys389Trp);(=)	0.0008127	–	VUS	VUS			
102	*PARN (NM_002582.4)*	c.(1693G>A);(=) p.(G565R);(=)	–	–	VUS	VUS			
32	*RTEL1 (NM_001283009.2)*	c.(3592G>A)(=) p.(Glu1198Lys);(=)	0.00004941	VCV000640501.4	VUS	VUS		Liver cirrhosis	
21	*TERT (NM_198253.3)*	c.(3007A>C);(=) p.(Lys1003Gln);(=)	–	–	VUS	VUS			
57	*TERT (NM_198253.3)*	c.(604G>A);(=) p.(A202T);(=)	0.00006545	VCV000012729.46	VUS (12); Benign (1);	VUS	AH		Sister

gnomAD : minor allele frequency reported in the non-Finnish European (NFE) subpopulation of the gnomAD database.[30]
ILD, interstitial lung disease; VUS, variants of uncertain significance.

prioritisation using the clinical IPF-related gene panel (online supplemental table 1), only **MUC5B** remained statistically significant (OR=443.14; 95% CI 38.03 to 62 795.73; false discovery rate (FDR)=3.71E–05).

Exploratory functional enrichment analysis

To provide biological context for the broader burden results, the 82 genes (figure 2) identified, without panel-based prioritisation, were examined using exploratory functional enrichment analyses.

Within this broader gene set, several enriched terms were related to ciliary structure and function (figure 3A; FDR <0.05; online supplemental figure S4). This enrichment was driven by rare predicted LoF variants observed across multiple patients with IPF in genes involved in cilium organisation and motility.

The main functional cluster involved cilium organisation and motility and included genes such as **DNAH5, DNAH6, DNAH7, DNAH9, HYDIN** and **NPHP4** (figure 3B). These genes contributed to multiple cilium-related GO terms, suggesting functional convergence within the unfiltered burden results.

Consistently, the STRING network analysis (https://string-db.org/) showed biological connections among genes involved in cytoskeleton-related and cilium-related processes (online supplemental figure 3). Within this broader exploratory signal, **HYDIN** was among the strongest individual gene-level associations identified by Firth logistic regression (OR=150.36; 95% CI 13.27 to 20 780.48; p=7.33E–06) (figure 2).

Additionally, the distribution of variants per sample (online supplemental figure S4A–C) confirms that most individuals carry one or two variants, with a progressively decreasing frequency as the number of variants increases. This distribution indicates that there is no bias due to gene aggregation, as variants are not concentrated in a single individual but rather consistently distributed across the samples, reinforcing the robustness of the adopted approach.

DISCUSSION

IPF is a progressive and fatal ILD with a multifactorial aetiology, arising from the interplay between genetic predisposition and environmental exposures.[33] In this study, we explored the contribution of rare genetic variants to IPF susceptibility in a Sardinian cohort.

Our first finding was the identification of pathogenic or likely pathogenic variants in telomere-maintenance genes in 14 (11.4%) of 123 patients, indicating that telomere-related genetic susceptibility is also detectable outside familial forms of IPF. Although this proportion is slightly lower than the 15%–20% frequency of rare telomere-related variants reported in family-enriched IPF cohorts,[8 23 34] our cohort was not restricted to familial disease. Notably, 7 of the 14 patients carrying a pathogenic or likely pathogenic telomere-related variant

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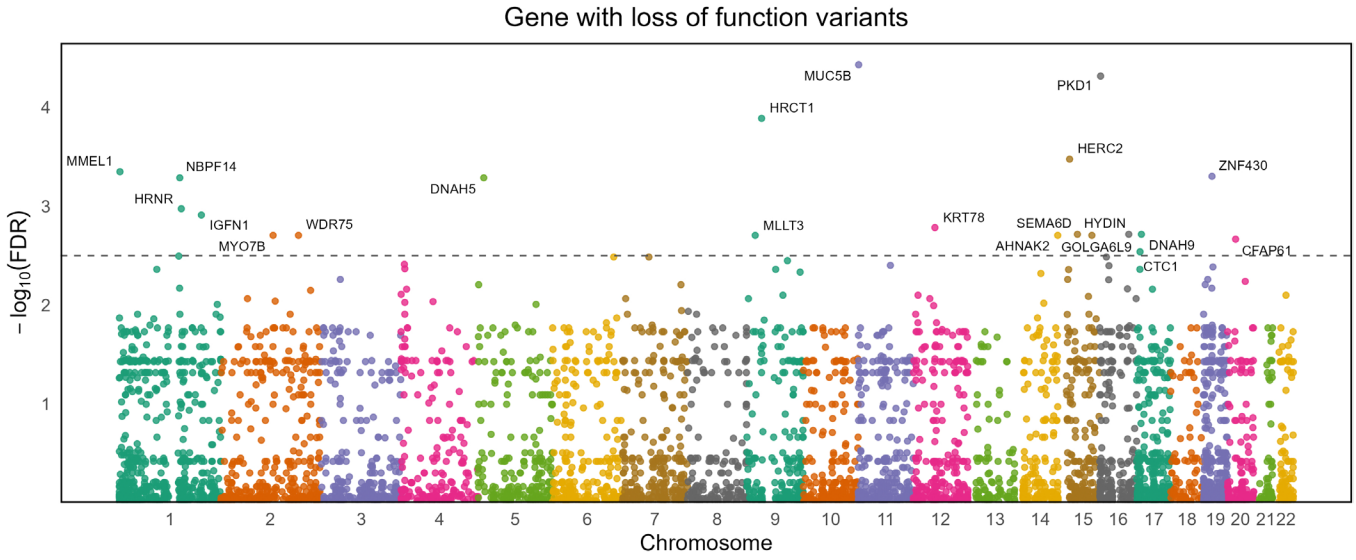

Figure 2 Manhattan plot Cohort Allelic Sums Test. The plot displays genes with different mutational burdens identified through Firth's logistic regression. The Benjamini-Hochberg method was applied, with a FDR threshold of 0.5%. FDR, false discovery rate.

reported a family history of ILD, whereas the remaining seven were apparently sporadic.

Consistent with the predominantly sporadic nature of our cohort, a family history of IPF was reported in 22 (17.9%) of 123 patients. Even within this smaller familial subgroup, a molecular diagnosis was achieved in only seven individuals, while 15 cases remained genetically unresolved. This observation is consistent with previous studies showing that a substantial proportion of familial pulmonary fibrosis cases remain without a clear genetic explanation after testing, with unresolved fractions ranging from approximately 30% to 60%.[35 36]

Telomere dysfunction has been well established as a contributing factor in IPF, although its role has been most clearly demonstrated in familial forms.[37] Telomeres are specialised nucleoprotein structures at the ends of chromosomes that progressively shorten with age, ultimately leading to cellular senescence and impaired regenerative capacity.

Consistent with previous cohorts, patients carrying pathogenic or likely pathogenic variants in telomere-maintenance genes showed a distinct clinical profile, characterised by earlier disease onset.[38] In our cohort, they also showed a higher prevalence of never-smokers compared with the negative group, a finding that may point to a relatively stronger contribution of genetic susceptibility in the absence of smoking exposure, although this finding requires confirmation in larger cohorts.

Clinical features suggestive of telomere biology disorders were uncommon overall, but premature greying of hair was observed only among carriers of pathogenic or likely pathogenic telomere-related variants, while liver cirrhosis, osteoporosis and myelodysplastic syndrome were each recorded only in isolated cases. Together, these observations support the presence of a broader telomere-related phenotype in at least a subset of patients.

By contrast, we did not observe significant differences in sex distribution, longitudinal pulmonary function decline, overall survival across WES-defined groups.

The relatively favourable survival observed in our cohort appears lower than that reported in many historical IPF series. This is relevant, because IPF has traditionally been associated with a median survival of about 3–5 years from diagnosis,[39] although more recent cohorts from the antifibrotic era have shown improved short-term outcomes. For example, more recent IPF cohorts have shown improved survival, with median survival increasing from 3 to 4 years across periods and 1year mortality reported to be lower in antifibrotic-treated than in untreated patients.[40] In our cohort, this more favourable survival may reflect the high proportion of patients receiving antifibrotic therapy, relatively preserved baseline lung function and the composition of a clinic-based cohort with longitudinal follow-up. Consistent with this interpretation, real-world registry data have reported lower estimated 1year mortality in antifibrotic-treated than in untreated patients with IPF.[41]

In particular, findings from human IPF cases and animal models have demonstrated an association between telomere dysfunction and the onset of pulmonary fibrosis, involving alveolar stem cells known as alveolar epithelial type 2 cell (AEC2).[42–44] Although this link has been established, the exact contribution of these cells in the progression of fibrotic lung disease is still not fully understood. While some animal studies indicate that AEC2 cellular senescence may drive disease progression,[45–47] others highlight AEC2 cell death as a key mechanism involved in the development of pulmonary fibrosis.[48] Senescent AEC2s are believed to influence surrounding

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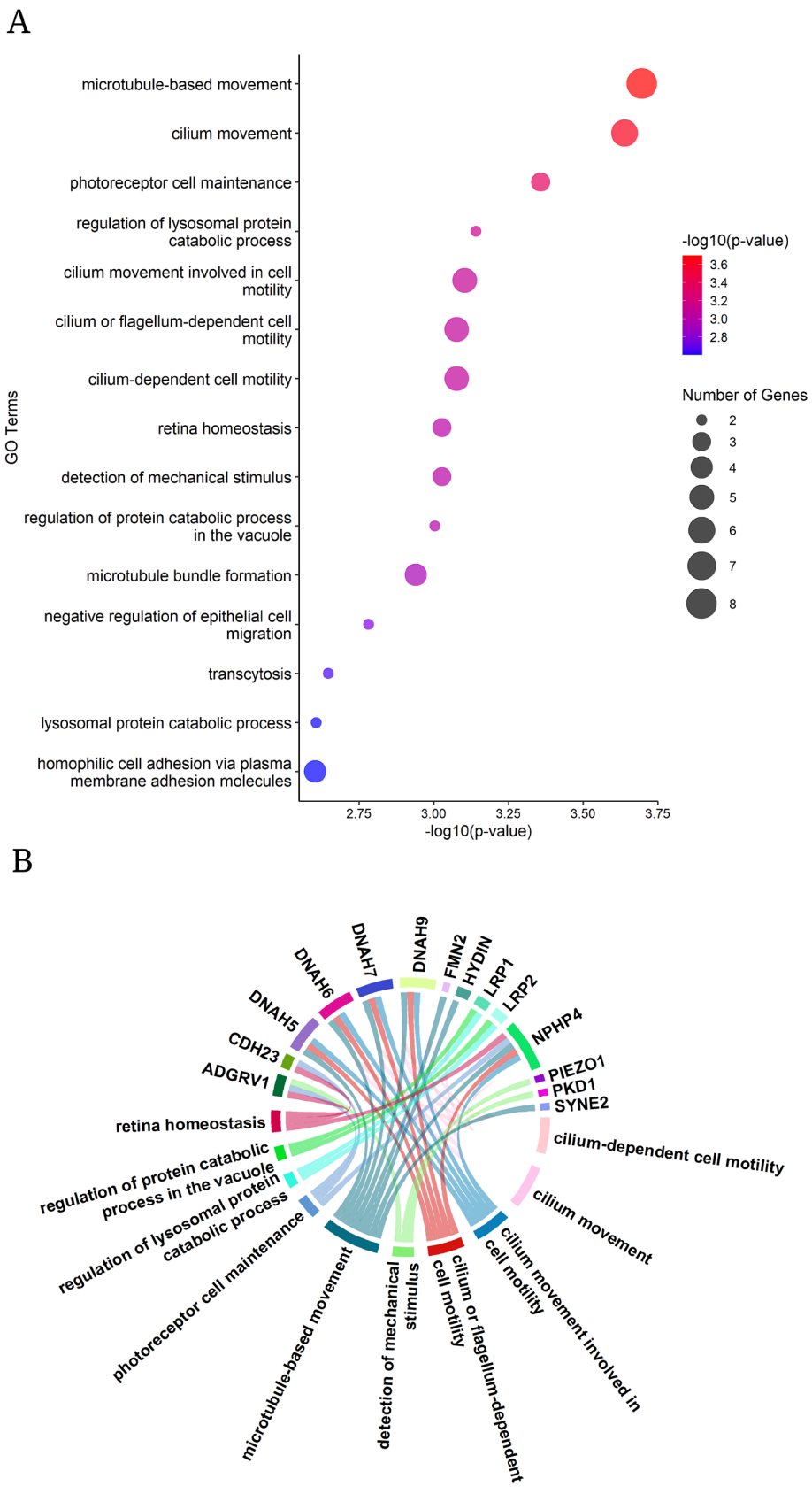

Figure 3 GO enrichment analysis: bubble diagram (A) and chord diagram (B). (A) The vertical axis represents the enriched Gene Ontology (GO) categories, while the horizontal axis indicates the proportion of mutated genes relative to the total number of human genes. A higher intensity of green colour corresponds to a more significant enrichment, while the size of the bubbles is proportional to the number of involved genes. (B) The chord diagram illustrates the relationships between the top 10 most significant GO terms and the hub genes.

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cells through the senescence-associated secretory phenotype.[47]

Additionally, various forms of AEC2 cell death—apoptosis, necrosis, necroptosis—can lead to the release of distinct cytokines. For instance, apoptotic cells produce IL-10 and TGF-β, necrotic cells release IL-1α, necroptotic cells secrete IL-8, IL-1, CXCL2 and cyclophilin A, while pyroptotic cells release IL-1β, IL-18, TNF-α and IL-6.[49] These secreted factors are thought to attract innate immune cells to clear dying cells and modulate inflammation and tissue repair. However, excessive production of IL-10 and TGF-β may contribute to the development of pulmonary fibrosis. Therefore, the roles of AEC2 senescence and cell death in the pathogenesis of pulmonary fibrosis warrant further exploration.

Of particular interest is that about half of the pathogenic variants were not found in public databases, highlighting the unique genetic background of the Sardinian population[28 50–53] (online supplemental materials).

Among the genes analysed, *CTC1* stands out due to the novelty and relevance of the findings. This gene was identified in two affected brothers, likely inherited from their mother who died of pulmonary fibrosis. Additionally, a variant in the same gene was found in an unrelated sporadic case. Although *CTC1* is known for its role in the conserved telomere maintenance component 1, its implication in IPF remains largely unexplored,[54] and it is currently not listed in the major genetic database Online Catalog of Human Genes and Genetic Disorders as being associated with IPF.[55] Furthermore, in ClinVar, most classified pathogenic variants in this gene are not directly linked to pulmonary fibrosis. However, recent studies indicate a possible connection between *CTC1* and IPF.[56–59] As a component of the CST complex, *CTC1* plays a key role in maintaining telomere structural integrity and has been identified as a candidate gene for IPF. To date, 51 variants have been reported, most of which are linked to *Coats plus syndrome or cerebroretinal microangiopathy with calcifications and cysts*,[54 60] both autosomal recessive conditions linked to telomere maintenance defects. So far, only few studies have reported heterozygous *CTC1* variants as potentially causative in patients with pulmonary fibrosis,[48 51] highlighting the evolving nature of the genetic landscape of the disease.

Beyond telomere-related genes, the CAST burden analysis highlighted a broader set of genes enriched for rare predicted LoF variants, several of which converged on pathways related to ciliary structure and motility, including, *DNAH5, DNAH6, DNAH7, DNAH9* and *HYDIN*.

Importantly, this analysis was performed on a subset of 99 unrelated IPF cases after excluding related cases and individuals of non-Sardinian ancestry, to reduce confounding due to relatedness and population stratification.

Moreover, this analysis extended beyond genes currently included in the clinical IPF-related diagnostic panel (online supplemental table S1) and was intended as an exploratory approach to assess whether the broader burden signal showed convergence on specific biological pathways. In this context, the observed enrichment of dynein-related and other cilium-associated genes may suggest a possible contribution of mucociliary dysfunction to sporadic IPF susceptibility in this population, rather than establishing these genes as validated susceptibility genes.

While biallelic mutations in these genes cause *primary ciliary dyskinesia*.[61] Although our patients do not present with the full LoF phenotype usually associated with these genes, it is plausible to hypothesise that a partial loss of function may occur, which could subtly impair mucociliary function.

Indeed, MCC plays a crucial role in removing mucus, debris and pathogens from the respiratory tract.[62] A partial deficiency in this mechanism could predispose to chronic infections and ongoing airway inflammation, both of which may contribute to fibrogenesis.

Recent studies have increasingly reported that heterozygous carriers of pathogenic variants associated with recessive diseases may present with mild and non-specific symptoms, particularly in the neurological, neuromuscular, haematological and pulmonary domains. These manifestations are generally milder and tend to emerge later in life than cases with biallelic variants.[63 64] Hypothesised mechanisms include genetic and environmental modifiers, digenic or oligogenic inheritance, skewed methylation patterns and mutational burden.

Environmental exposure appears to play a crucial role. For instance, *MZ* heterozygotes for alpha-1 antitrypsin have an increased risk of developing pulmonary disease in the presence of cigarette smoking or occupational exposure to pollutants, mineral dust, gas and fumes. In Hereditary haemochromatosis type 1 (HFE-related haemochromatosis) disorders, a high phenotypic variability among homozygotes and heterozygotes for the p.His63Asp variant has been observed. In these cases, environmental factors such as excessive alcohol intake and viral hepatitis have been identified as potential modifiers of clinical expression.[65]

The type of variant also appears to be relevant. Although available data are still limited,[66] dominant effects may arise from protein haploinsufficiency, namely the inability of a single functional allele to ensure adequate protein production.[67] In such cases, symptoms in heterozygotes are often milder and have a later onset compared with homozygotes or compound heterozygotes,[68] suggesting the possibility of a ‘pseudodominant inheritance’ pattern.

In our cases, therefore, haploinsufficiency of microtubule-associated motor proteins could predispose to persistent airway inflammation, potentially involved in fibrogenesis.

Previous studies have shown that the expression of cilium-related genes defines two distinct molecular phenotypes in IPF/UIP.[69] Patients with high expression of ciliary genes exhibit increased microscopic honeycombing and elevated tissue expression of *MUC5B* and *MMP7*, suggesting a more fibrotic tissue phenotype.[69] Other studies have hypothesised that IPF is a mucociliary

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disease caused by recurrent injury and aberrant repair at the bronchoalveolar junction, initiated and exacerbated by *MUC5B* overexpression. This leads to impaired ciliary function, particle retention and increased tissue damage.[70] In our study, we identified a series of rare LoF variants in genes involved in this pathway.

Furthermore, key developmental signalling pathways regulated by the primary cilium, such as Sonic Hedgehog,[71 72] fibroblast growth factor,[73 74] platelet-derived growth factor[75 76] and canonical/non-canonical Wnt-signalling,[77 78] have been implicated in IPF pathogenesis. Disruption of these pathways through ciliary gene variants could directly contribute to aberrant tissue remodelling and fibrotic progression.

In our study, the strong signal observed for *MUC5B* in the CAST analysis (OR=443.14; 95% CI 38.03 to 62 795.73; FDR=6.81E–07) (figure 2) is of particular interest.

While previous studies have focused on a common promoter polymorphism (*rs35705950*) associated with *MUC5B* overexpression and increased IPF risk,[79] our findings revealed LoF variants in the gene's coding regions (online supplemental table 3).

These therefore represent different classes of genetic variation and may reflect distinct biological mechanisms. However, formal assessment of independence from the common promoter signal was not possible with our exome-based dataset.

The functional consequences of these identified missense variants remain unclear, as they may not cause complete LoF but instead alter protein structure or activity. Unlike the well-characterised gain-of-function (GoF) effect associated with *rs35705950*, the impact of these rare variants may be distinct.

The coexistence of both GoF and potentially LoF coding variants suggests a more complex, possibly dose-sensitive role for *Muc5b* in maintaining lung homeostasis. Indeed, reduction in *MUC5B* expression may also impair MCC, thereby contributing to disease pathogenesis. Supporting this hypothesis, studies in mice have shown that complete or partial loss of *Muc5b* leads to marked reductions in MCC, even in heterozygous animals that produce ~50% of the wild-type levels.[80] Additionally, human studies have reported biallelic *MUC5B* LoF variants associated with airway disease phenotypes and diminished protein levels in airway mucus.[81] These observations underscore the crucial role of *MUC5B* in maintaining normal mucociliary function and airway homeostasis, where both overexpression and downregulation may act as predisposing factors for disease development.

A limitation of this study is that the control cohort was not systematically phenotyped for subclinical respiratory abnormalities; therefore, asymptomatic interstitial lung abnormalities (ILAs) could not be excluded. Given the reported prevalence of ILAs in adults,[82] a small number of controls may have harboured unrecognised subclinical interstitial changes. However, not all ILAs progress to clinically significant ILD, and progression appears to be limited to only a subset of individuals.[83] This potential misclassification would likely bias the analysis towards the null, making the observed associations more conservative rather than inflated.

A further limitation is the relatively small size of our cohort, which reduces statistical power and means that some findings should be regarded as exploratory. However, studies in genetically homogeneous founder populations have shown that reduced allelic heterogeneity and extended linkage disequilibrium can increase power per participant, allowing the detection of associations with smaller sample sizes than would typically be required in more heterogeneous outbred populations.[84]

In conclusion, our findings confirm the contribution of pathogenic variants in telomere-related genes in IPF pathogenesis. The identification of *CTC1* variants in both familial and sporadic cases, along with a high proportion of previously unreported variants, underscores the genetic uniqueness of the Sardinian population and highlights the evolving genetic landscape of IPF.

Moreover, the burden analysis suggested pathway-level convergence of rare predicted LoF variants in genes related to ciliary structure and mucociliary function, particularly dynein-related genes. Although these findings were exploratory and require replication, they raise the possibility that altered mucociliary homeostasis may contribute to IPF susceptibility in this Sardinian cohort. The potential for these variants to induce partial impairment of MCC suggests a contributing role in chronic airway injury, persistent inflammation and fibrogenesis. These manifestations, generally milder and with later onset compared with individuals carrying biallelic variants in dynein-related genes, suggest a possible scenario of 'pseudodominant inheritance'.

Importantly, the strong signal observed in the *MUC5B* gene further emphasises its pivotal role in mucociliary homeostasis. This observation supports emerging hypotheses that IPF may, at least in part, represent a disorder of mucociliary dysfunction. Overall, these findings broaden the current understanding of IPF biology, although validation in larger and independent cohorts will be necessary before broader clinical implications can be inferred.

Author affiliations
[1]Medical Genetics, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[2]Centre for Research University Services (CeSAR, Centro Servizi di Ateneo per la Ricerca), University of Cagliari, Cagliari, Italy
[3]Medical Genetics, R. Binaghi Hospital, Cagliari, Italy
[4]Pneumology Unit, R. Binaghi Hospital, Cagliari, Italy
[5]Pediatric Clinic and Rare Diseases, Microcitemico Hospital "A.Cao", Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
[6]Oncology and Molecular Pathology Unit, Department of Biomedical Sciences, University of Cagliari, Cagliari, Italy
[7]Department of Biomedical Sciences, University of Sassari, Sassari, Italy
[8]Unit of Medical Genetics, University Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy

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Patient consent for publication Not applicable.

Ethics approval Patient recruitment and enrolment were conducted at the Department of Biomedical Sciences and Public Health, University of Cagliari, and the Department of Pulmonology, Binaghi Hospital (ASL Cagliari, Italy). All patients and controls provided written informed consent in accordance with institutional and national ethical standards set by the local human research ethics committee. The study protocol was approved by the Sardinian Ethics Committee (approval date: 4 May 2023; protocol number 18 04/05/2023) and follows the ethical principles of the Declaration of Helsinki. Informed consent documents are securely stored in hospital records and are part of each patient's medical file. Participants gave informed consent to participate in the study before taking part.

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ORCID iD

Matteo Floris https://orcid.org/0000-0003-4385-9336

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