Poster

Gene-based collapsing genetic analyses to identify rare protein-coding variants associated with susceptibility to idiopathic pulmonary fibrosis (IPF): data from the IPF-PRO Registry

American Thoracic Society (ATS) International Conference

May 13-18, 2022

SC-US-74360

Gene-based collapsing genetic analyses to identify rare protein-coding variants associated with susceptibility to idiopathic pulmonary fibrosis (IPF): data from the IPF-PRO Registry

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INTRODUCTION

- Prior research suggests that rare mutations in protein-coding regions of genes involved in telomere maintenance contribute to the development of familial pulmonary fibrosis and confer risk for sporadic IPF.[1-3]

AIM

- To understand further the importance of rare protein-coding variants in determining the risk of IPF.

METHODS

- The IPF cohort comprised **908 patients from the IPF-PRO Registry**, a multi-center US registry of patients with IPF.[4] The control cohort comprised **24,749 controls without lung disease**.
- WGS of the IPF cohort and **WGS or whole exome sequencing** of the controls was performed at the Columbia University Institute for Genomic Medicine.
- We implemented a **gene-based collapsing test** to identify genes with a significant difference between the IPF cohort and the controls in the proportion of individuals carrying at least one **qualifying variant (QV)** in the gene.
  - A QV was defined as a variant that met specific filter criteria based on population allele frequency and predicted variant effect.
  - For each gene, a two-sided Cochran-Mantel-Haenszel test was used to compare the rate of patients with IPF carrying a QV with the rate observed in controls while controlling for ancestry.
- In addition, we examined the association of 15 common genetic variants associated with IPF in 908 patients from the IPF-PRO Registry and 3034 controls. Single-variant analyses were conducted using logistic regression with an additive model and sex plus the first 10 principal components as covariates.

CONCLUSIONS

- These data support the idea that rare protein-coding mutations in telomere-related genes play a role in determining susceptibility to IPF, including sporadic IPF.
- Future work will apply novel methods to the WGS data from this cohort to evaluate the role of regulatory variants in non-coding regions in determining IPF susceptibility or behavior.

RESULTS

Baseline characteristics of cohort overall and stratified by QV carrier status

	All patients (N=908)	QV+ (N=61)	QV- (N=847)
Age (years)	70.7 (65.5, 75.4)	65.9 (60.6, 69.2)	71.0 (65.9, 75.7)
Male	686 (75.6)	45 (73.8)	641 (75.7)
Race			
White	836 (94.1)	57 (93.4)	779 (94.2)
Black or African-American	17 (1.9)	0 (0)	17 (2.1)
Other	35 (3.9)	4 (6.6)	31 (3.7)
Hispanic or Latino ethnicity	34 (3.7)	2 (3.3)	32 (3.8)
Ever smoker	607 (66.9)	28 (45.9)	579 (68.4)
Family history of ILD	166 (18.3)	24 (39.3)	142 (16.8)
Definite IPF[5]	590 (65.0)	42 (68.9)	548 (64.7)
FVC % predicted*	69.5 (59.3, 80.2)	65.6 (52.4, 78.0)	69.7 (59.8, 80.5)
DLco % predicted*	41.9 (32.3, 50.2)	41.2 (32.2, 49.5)	41.9 (32.5, 50.5)
GAP stage[6]*			
1	227 (28.5)	17 (30.9)	210 (28.3)
2	430 (54.0)	30 (54.5)	400 (54.0)
3	139 (17.5)	8 (14.5)	131 (17.7)
Oxygen at rest*	179 (20.1)	11 (18.6%)	168 (20.2)
Oxygen with activity*	305 (34.4)	23 (39.0)	282 (34.1)
Antifibrotic drug use	502 (55.3)	30 (49.1)	472 (55.8)

Data are n(%) or median (Q1, Q3).
*Among those with available data.

Quantile-quantile plot of a gene-based collapsing analysis under a Rare-Ensemble model

The model considered only dominant loss of function variants and missense variants predicted to be damaging by an ensemble of Polyphen, REVEL, and PrimateAL. All variants had an internal minor allele frequency < 0.005% in public databases (gnomAD and ExAC). The yellow and light blue lines indicate the 2.5th and 97.5th percentiles of the expected p-values.

Rare protein-coding variants associated with susceptibility to IPF

- In gene-based collapsing analysis of protein-coding variants, telomere-related genes *TERT*, *PARN* and *RTEL1* achieved study-wide significance.

Qualifying variants in patients with IPF and controls

	IPF	Controls	Odds ratio (95% CI)	P-value
TERT	3.1%	0.1%	35.2 (17.6, 72.2)	5.7×10^{-25}
PARN	1.8%	0.1%	22.7 (10.2, 50.0)	1.4×10^{-13}
RTEL1	2.0%	0.3%	6.8 (3.7, 12.2)	8.5×10^{-9}

Characteristics of QV carriers compared to non-carriers

Younger

Less likely to have a history of smoking

More likely to have family history of ILD

Common genetic variants associated with IPF

Gene	SNP	Risk allele	Odds ratio (95% CI)	P-value
MUC5B	rs35705950	T	6.40 (5.47, 7.49)	1.26×10^{-118}
TOLLIP	rs111521887	G	1.91 (1.67, 2.18)	1.93×10^{-21}
TOLLIP	rs5743894	C	1.89 (1.66, 2.16)	4.90×10^{-21}
DSP	rs2076295	G	1.45 (1.30, 1.61)	1.54×10^{-11}
TERT	rs2736100	C	0.69 (0.62, 0.77)	3.35×10^{-11}

Variants investigated; MUC5B rs35705950, TOLLIP rs111521887, TOLLIP rs5743894, DSP rs2076295, TERT rs2736100, TOLLIP rs5743890, DEPTOR rs28513081, SPDL1 rs116483731, RTEL1 rs41308092, KIF15 rs78238620, SPPL2C rs17690703, MAD1L1 rs12699415, MDGA2 rs7144383, HECTD2 rs537322302, AKAP13 rs62025270.

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ACKNOWLEDGEMENTS AND DISCLOSURES

The IPF-PRO/ILD-PRO Registry is funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) and coordinated by the Duke Clinical Research Institute. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment for the development of this poster. Wendy Morris of FleishmanHillard, London, UK, provided editorial and formatting assistance, which was contracted and funded by BIPI. BI was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations. Gundula Povysil has no conflicts of interest. Jamie Todd has received grants from the National Institutes of Health, AstraZeneca, BI, CareDx and has served on advisory boards for Natera and Altavant Sciences. Scott Palmer has received grants from AstraZeneca, Bristol Myers Squibb, CareDx; royalties from UpToDate; fees from Altavant Sciences and Bristol Myers Squibb. Jamie Todd and Scott Palmer are employees of DCRI, which receives funding support from BIPI to coordinate the IPF-PRO/ILD-PRO Registry.

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IPF-PRO Registry enrolling centers: Albany Medical Center, Albany, NY; Baylor College of Medicine, Houston, TX; Baylor University Medical Center at Dallas, Dallas, TX; Cleveland Clinic, Cleveland, OH; Columbia University Medical Center/New York Presbyterian Hospital, New York, NY; Duke University Medical Center, Durham, NC; Froedtert & The Medical College of Wisconsin Community Physicians, Milwaukee, WI; Houston Methodist Lung Center, Houston, TX; Lahey Clinic, Burlington, MA; Loyola University Health System, Maywood, IL; Lynchburg Pulmonary Associates, Lynchburg, VA; Medical University of South Carolina, Charleston, SC; National Jewish Health, Denver, CO; NYU Medical Center, New York, NY; Piedmont Healthcare, Austell, GA; Pulmonary Associates of Stamford, Stamford, CT; Pulmonix LLC, Greensboro, NC; Renovatio Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical Research Center, Winston Salem, NC; South Miami Hospital, South Miami, FL; St. Joseph's Hospital, Phoenix, AZ; Stanford University, Stanford, CA; Temple University, Philadelphia, PA; The Oregon Clinic, Portland, OR; Tulane University, New Orleans, LA; UNC Chapel Hill, Chapel Hill, NC; University of Alabama at Birmingham, Birmingham, AL; University of California, Davis, Sacramento, CA; University of California Los Angeles, Los Angeles, CA; University of Chicago, Chicago, IL; University of Cincinnati Medical Center, Cincinnati, OH; University of Louisville, Louisville, KY; University of Miami, Miami, FL; University of Michigan, Ann Arbor, MI; University of Minnesota, Minneapolis, MN; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburgh, PA; University of Virginia, Charlottesville, VA; UT Southwestern Medical Center, Dallas, TX; Vanderbilt University Medical Center, Nashville, TN; Vermont Lung Center, Colchester, VT; Wake Forest University, Winston Salem, NC; Washington University, St. Louis, MO; Weill Cornell Medical College, New York, NY; Wilmington Health and PMG Research, Wilmington, NC; Yale School of Medicine, New Haven, CT.

Poster presented at the American Thoracic Society International Conference, 2022.
SC-US-74360