



- 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
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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. Singlevariant analyses were conducted using logistic regression with an additive model and sex plus the first 10 principal components as covariates.

CONCLUSIONS

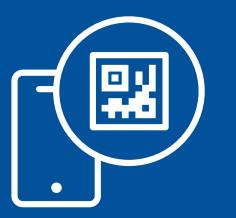
- These data support the idea that rare protein-coding mutations in telomererelated genes play a role in determining susceptibility to IPF, including sporadic IPF.
- Future work will apply novel methods to the WGS data from this cohort to evaluate the role of regulatory variants in non-coding regions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

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	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
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
DLco % predicted*	41.9 (32.3, 50.2)	41.2 (32.2, 49.5)	41.9 (32.5, 50
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)

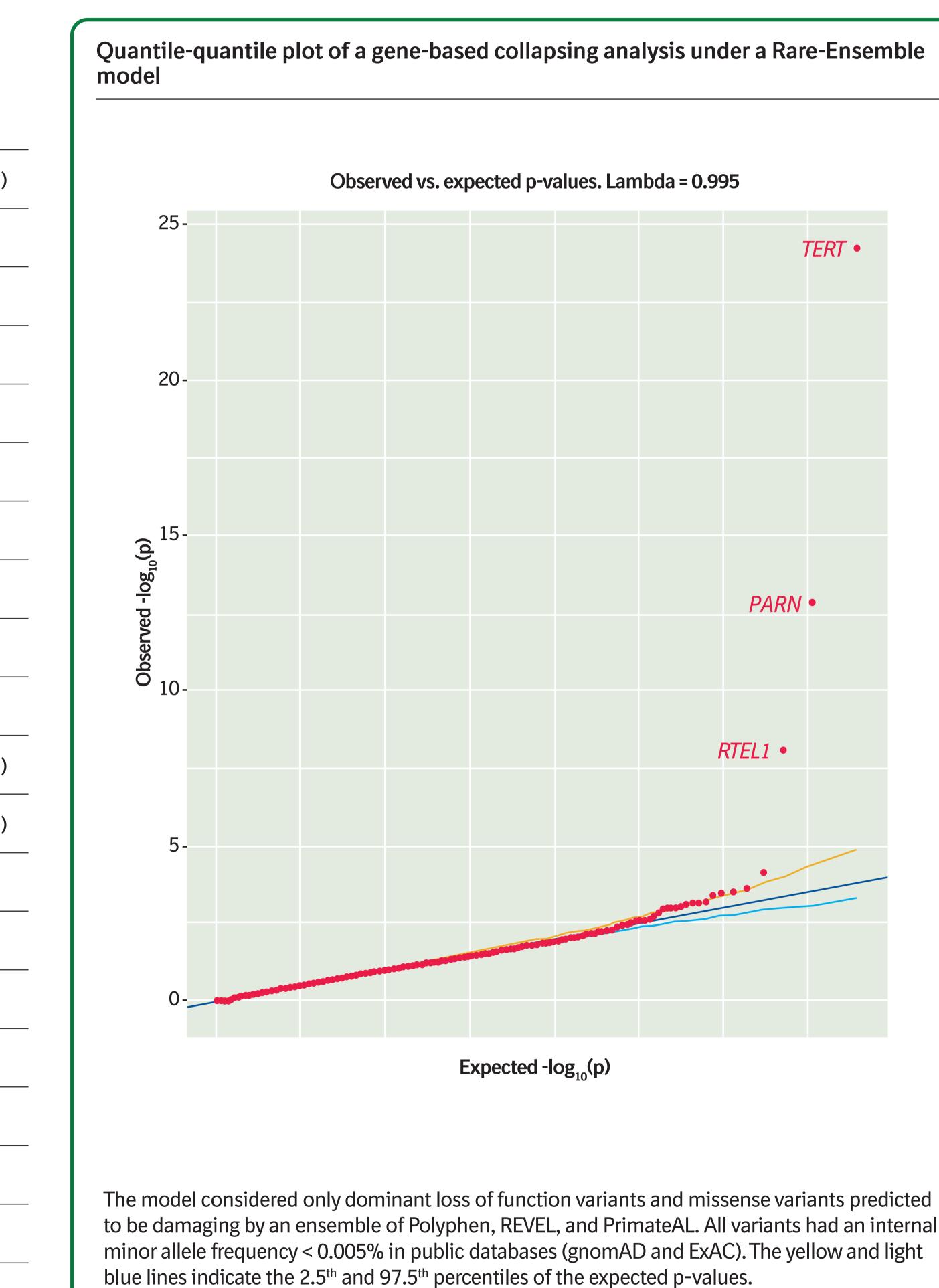
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IPF-PRO Registry enrolling centers: Albany Medical Center, Albany, NY; Baylor College of Medical Center, Albany, NY; Baylor College of Medical Center, New York, NY; Duke University Medical Center, Durham, NC; Froedtert & The Medical College of Wisconsin Community Physicians, Milwaukee, WI; Houston Methodist Lung Center, Houston, TX; Lahey Clinic, Burlington, MA; Loyola University of South Carolina, Charleston, SC; National Jewish Health, Denver, CO; NYU Medical Center, New York, NY; Piedmont Healthcare, Austell, GA; Pulmonary Associates of Stamford, CT; PulmonIx LLC, Greensboro, NC; Renovatio Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical, South Miami, FL; St. Joseph's Hospital, South Chest and Southeastern Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical, The Woodlands, TX; Salem Chest and Southeastern Clinical, South Anisot, South Anisot, South Chest and Southeastern Clinical, South Anisot, Sout Philadelphia, PA; The Oregon Clinic, Portland, OR; Tulane University of California, Davis, Sacramento, CA; University of California Los Angeles, CA; University of Chicago, IL; University of Cincinnati Medical Center, Cincinnati, OH; University of Louisville, Louisville, KY; University of Miami, FL; University of Minnesota, Mi 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.

RESULTS



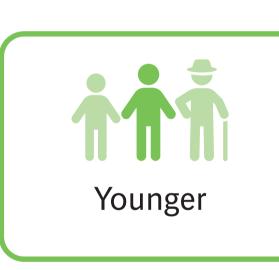


Rare protein-coding variants associated with susceptibility to IPF

• 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		
3.1%	0.1%	35.2 (17.6, 72.2)	5.7 × 10 ⁻²⁵		
1.8%	0.1%	22.7 (10.2, 50.0)	1.4 × 10 ⁻¹³		
2.0%	0.3%	6.8 (3.7, 12.2)	8.5 × 10 ⁻⁹		
	IPF 3.1% 1.8%	IPF Controls 3.1% 0.1% 1.8% 0.1%	IPF Controls Odds ratio (95% CI) 3.1% 0.1% 35.2 (17.6, 72.2) 1.8% 0.1% 22.7 (10.2, 50.0)		

Characteristics of QV carriers compared to non-carriers







Common genetic variants associated with IPF

Gene	SNP	Risk allele	Odds ratio (95% CI)	P-value
MUC5B	rs35705950	Т	6.40 (5.47, 7.49)	1.26 x10 ⁻¹¹⁸
TOLLIP	rs111521887	G	1.91 (1.67, 2.18)	1.93x10 ⁻²¹
TOLLIP	rs5743894	С	1.89 (1.66, 2.16)	4.90x10 ⁻²¹
DSP	rs2076295	G	1.45 (1.30, 1.61)	1.54x10 ⁻¹¹
TERT	rs2736100	С	0.69 (0.62, 0.77)	3.35x10 ⁻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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