Poster

Association of genetic variants with disease progression in patients with idiopathic pulmonary fibrosis (IPF): data from the IPF-PRO Registry

American Thoracic Society (ATS) International Conference

May 13-18, 2022

SC-US-74359

P

Association of genetic variants with disease progression in patients with idiopathic pulmonary fibrosis (IPF): data from the IPF-PRO Registry

Jamie L Todd,[1,2] Gundula Povysil,[3] Andrew S Allen,[1] Daniel F Dilling,[4] Hyun J Kim,[5] Megan L Neely,[1,2] Imre Noth,[6] Zhong Ren,[3] Laurie D Snyder,[1,2] Mary E Strek,[7] Aparna Swaminathan,[1,2] David Zhang,[8] Christian Hesslinger,[9] Thomas B Leonard,[10] David B Goldstein,[8] Scott M Palmer[1,2] on behalf of the IPF-PRO Registry investigators

[1]Duke Clinical Research Institute, Durham, NC, USA; [2]Duke University Medical Center, Durham, NC, USA; [3]Institute for Genomic Medicine, Columbia University, New York, NY, USA; [4]Division of Pulmonary and Critical Care, Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA; [5]University of Minnesota, Minneapolis, MN, USA; [6]Division of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, VA, USA; [7]Section of Pulmonary, Critical Care Medicine, University of Chicago, Chicago, IL, USA; [8]Columbia University Irving Medical Center, New York, NY, USA; [9]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [10]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA.

INTRODUCTION

- Genetic variants, including those in the telomere-related genes *TERT*, *RTEL1* and *PARN* and the *MUC5B* risk allele (rs35705950G>T), have been associated with susceptibility to IPF.[1,2]
- In patients with IPF, the *MUC5B* risk allele has been associated with improved survival, while shorter telomere lengths are associated with worse survival.[3,4]

AIM

- We performed whole genome sequencing (WGS) in a cohort of patients with IPF to examine the influence of select genetic variants and telomere length on disease progression.

METHODS

- WGS was performed on DNA from **908 patients in the IPF-PRO Registry**, a multicenter US registry of patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months.[5]
- Telomere lengths were estimated using TelSeq[6] and the cohort divided into shorter vs. longer telomere groups based on values below vs. above the median.
- Using data from **24,749 controls without lung disease** in a gene-based collapsing analysis framework, 61 patients were identified as carrying a rare protein-coding IPF-associated **qualifying variant (QV)** with a predicted deleterious effect in *TERT*, *RTEL1*, or *PARN*.
- Kaplan-Meier analyses were used to describe **event-free survival** (where an event was defined as ≥10% decline in forced vital capacity % predicted, death, or lung transplant) over two years of follow-up across **strata of 1) telomere length, 2) carrier status of a QV in *TERT*, *RTEL1* or *PARN*, 3) carrier status of the *MUC5B* risk allele** (rs35705950G>T). The log-rank test was used for comparisons.

CONCLUSIONS

- In patients with IPF, rare protein-coding variants in *TERT*, *RTEL1* and *PARN* are associated with an increased risk of disease progression, even after accounting for the influence of the *MUC5B* risk allele and telomere length.
- Defining the influence of genetic and molecular features on outcomes in patients with IPF may improve prognostic models and clinical trial design.

RESULTS

Associations among qualifying variants (QV), telomere length, and age

- Patients with a QV in *TERT*, *RTEL1*, or *PARN* had shorter telomere lengths than those without a QV in one of these genes (median length: 3.47 kb vs. 3.82 kb; p=2.7x10^{-8}).
- There was no significant correlation between age and telomere length among patients with a QV in *TERT*, *RTEL1*, or *PARN* (r=0.13, p=0.32), but among those without a QV in these genes, telomere length decreased with increasing age (r = -0.1, p=0.004).

Baseline characteristics of patients with IPF stratified by QV carrier status

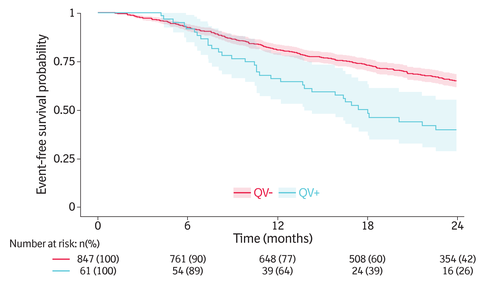
	QV+ (N=61)	QV- (N=847)
Age (years)	65.9 (60.6, 69.2)	71.0 (65.9, 75.7)
Male	45 (73.8)	641 (75.7)
Race		
White	57 (93.4)	779 (94.2)
Black or African-American	0 (0)	17 (2.1)
Other	4 (6.6)	31 (3.7)
Hispanic or Latino ethnicity	2 (3.3)	32 (3.8)
Ever smoker	28 (45.9)	579 (68.4)
Family history of ILD	24 (39.3)	142 (16.8)
Definite IPF[7]	42 (68.9)	548 (64.7)
FVC % predicted*	65.6 (52.4, 78.0)	69.7 (59.8, 80.5)
DLco % predicted*	41.2 (32.2, 49.5)	41.9 (32.5, 50.5)
GAP stage[8]*		
1	17 (30.9)	210 (28.3)
2	30 (54.5)	400 (54.0)
3	8 (14.5)	131 (17.7)
Oxygen at rest*	11 (18.6%)	168 (20.2)
Oxygen with activity*	23 (39.0)	282 (34.1)
Antifibrotic drug use	30 (49.1)	472 (55.8)

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

Impact of telomere length and QV on progression of IPF

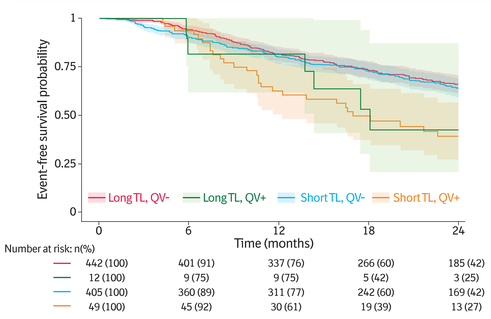
- Patients carrying a QV in *TERT*, *RTEL1*, or *PARN* had significantly worse outcomes over two years than patients without a QV (log-rank p=4.58x10^{-5}).

Event-free survival probability by QV carrier status



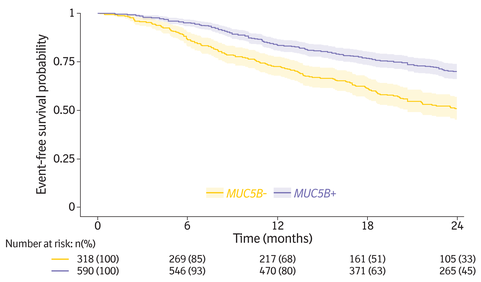
- There was no significant difference in event-free survival between patients with shorter vs. longer telomere length. The influence of QV carrier status on event-free survival was observed irrespective of telomere length.

Event-free survival probability by QV carrier status and telomere length (TL)



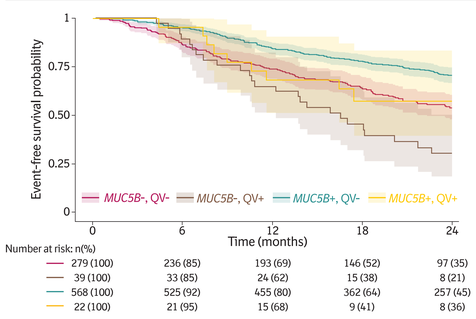
- Patients with the *MUC5B* risk allele had significantly better event-free survival than those without this allele (log-rank p=7.39x10^{-9}).

Event-free survival probability by *MUC5B* risk allele carrier status



- Patients without a QV in *TERT*, *RTEL1*, or *PARN*, but with the *MUC5B* risk allele had the best outcomes, while patients with a QV in *TERT*, *RTEL1*, or *PARN*, and without the *MUC5B* risk allele had the worst outcomes (log-rank p=1.06x10^{-9}).

Event-free survival probability by QV and *MUC5B* risk allele carrier status



REFERENCES

1. Petrovski S et al. Am J Respir Crit Care Med 2017;196:82–93.
2. Allen RJ et al. Am J Respir Crit Care Med 2020;201:564–574.
3. Stuart BD et al. Lancet Respir Med 2014;2:557–65.
4. Peljto AL et al. JAMA 2013;309:2232–2239.
5. O'Brien EC et al. BMJ Open Respir Res 2016;3:e000108.
6. Ding Z et al. Nucleic Acids Res 2014;42:e75.
7. Raghu G et al. Am J Respir Crit Care Med 2011;183:788–824.
8. Ley B et al. Ann Intern Med 2012;156:684–91.

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. Elizabeth Ng and 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. 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, Aparna Swaminathan and Scott Palmer are employees of DCRI, which receives funding support from BIPI to coordinate the IPF-PRO/ILD-PRO Registry.

Scan QR code or visit URL for a webpage featuring all BI-supported publications at ATS 2022.

https://www.usscicomms.com/respiratory/ATS2022

Scan QR code or visit URL for a device-friendly version of this poster.

https://www.usscicomms.com/respiratory/ATS2022/Todd2/

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-74359