5. Bourbeau J, Doiron D, Biswas S, Smith BM, Benedetti A, Brook JR, *et al.* Ambient air pollution and dysanapsis: associaitons with lung function and chronic obstructive pulmonary disease in the Canadian Cohort Obstructive Lung Disease study. *Am J Respir Crit Care Med* 2022;206: 44–55.
6. Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, *et al.*; MESA Lung, CanCOLD, and SPIROMICS Investigators. Association of dysanapsis with chronic obstructive pulmonary disease among older adults. *JAMA* 2020;323:2268–2280.
7. Adam M, Schikowski T, Carsin AE, Cai Y, Jacquemin B, Sanchez M, *et al.* Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. *Eur Respir J* 2015;45:38–50.
8. Paulin L, Hansel N. Particulate air pollution and impaired lung function. *F1000Res* 2016;5:F1000 Faculty Rev-201.
9. Phalen RF, Oldham MJ, Nel AE. Tracheobronchial particle dose considerations for in vitro toxicology studies. *Toxicol Sci* 2006;92: 126–132.
10. Hofmann W. Modelling inhaled particle deposition in the human lung—A review. *J Aerosol Sci* 2011;42:693–724.
11. Balásházy I, Hofmann W, Heistracher T. Local particle deposition patterns may play a key role in the development of lung cancer. *J Appl Physiol* 2003;94:1719–1725.
12. Mirabelli MC, Künzli N, Avol E, Gilliland FD, Gauderman WJ, McConnell R, *et al.* Respiratory symptoms following wildfire smoke exposure: airway size as a susceptibility factor. *Epidemiology* 2009;20: 451–459.
13. Hansel NN, Putcha N, Woo H, Peng R, Diette GB, Fawzy A, *et al.* Randomized clinical trial of air cleaners to improve indoor air quality and chronic obstructive pulmonary disease health: results of the CLEAN AIR study. *Am J Respir Crit Care Med* 2022;205: 421–430.
14. van Boven FE, de Jong NW, Braunstahl GJ, Arends LR, Gerth van Wijk R. Effectiveness of the air purification strategies for the treatment of allergic asthma: a meta-analysis. *Int Arch Allergy Immunol* 2020;181: 395–402.

Genetic Association Study Advances Idiopathic Pulmonary Fibrosis Pathophysiology and Health Equity

Idiopathic pulmonary fibrosis (IPF) is a devastating lung disease that, despite the advent of antifibrotic agents, urgently needs additional research to discover new pathobiology to unearth novel therapeutic pathways. Human genetics support for drug targets increases the chance that related drugs will be approved as novel therapies (1). IPF susceptibility is partially attributable to genetics, with ∼20% of all IPF cases being familial (two or more IPF cases noted in a family) and with common genetic variants explaining ∼30% or more of the risk of sporadic IPF (2). Genome-wide association studies (GWASs) offer an unbiased approach to identify population-level common genetic variants associated with IPF, and the most recent IPF GWAS reported a total of 14 genetic regions associated with IPF, including novel associations at three loci including a variant (rs78238620) near *KIF15* (kinesin family member 15) (3). Although GWASs are a powerful tool for the robust association of genetic variation with disease, the majority of GWAS associations fall in noncoding regions of the genome, making translation of genetic associations to disease-causing genes and disease-relevant biologic function difficult. By contrast, studies of nonsynonymous (i.e., associated with a change in protein structure) rare genetic variants allow for the direct assignment of a genetic association with a putative causal gene. Genetic studies of familial and sporadic IPF using targeted sequencing of candidate regions as well as whole-exome sequencing have identified IPF-associated rare genetic variants in surfactant protein genes and telomere-related genes, including *TERT*, *TERC*, *RTEL1*, *PARN*, and others (4–6).

In this issue of *Journal*, Zhang and colleagues (pp. 56–69) report the largest-to-date IPF genetic association analysis of rare deleterious protein-coding genetic variants (7). The authors used whole-exome and whole-genome sequencing of international multiple-ancestry familial and sporadic IPF cohorts with ∼3,250 total IPF cases included in the overall meta-analysis. In addition to replicating prior rare deleterious variant IPF associations in the telomere-related genes *TERT*, *PARN*, and *RTEL1*, the authors for the first time reported an excess number of rare deleterious *KIF15* variants in IPF cases compared with controls. The enrichment of rare deleterious *KIF15* variants in IPF cases is interesting considering the above-mentioned common variant IPF GWAS locus near *KIF15* (3). The IPF GWAS locus near *KIF15* had yet to be convincingly mapped to a causative gene. Finding rare variants of large effect in a gene near a common variant GWAS locus is not typical and significantly advances our knowledge of the pathobiology of IPF. *KIF15* is in the kinesin family and participates in the bipolar spindle assembly, which is essential to cell division (8). Zhang and colleagues performed functional studies demonstrating that decreased KIF15 protein expression reduced proliferation of lymphoblastoid cells heterozygous for the *KIF15* common variant rs78238620. Furthermore, the authors analyzed publicly available human lung single-cell RNA-sequencing data to demonstrate that *KIF15* gene expression is present in replicating epithelial and resident immune cells in the lungs. Together, these findings provide baseline functional evidence of common and rare genetic variants in and around *KIF15* perturbing a telomerase-independent pathway germane to the pathobiology of IPF.

The manuscript by Zhang and colleagues represents a significant advance in the study of genetic susceptibility to IPF; however, it also presents an opportunity to highlight the

Supported by a grant from Bayer and NIH NHLBI grants K08 HL136928, U01 HL089856, R01 HL135142, R01 HL139634, and R01 HL147148.

Originally Published in Press as DOI: 10.1164/rccm.202203-0612ED on May 3, 2022

propagation of racial and/or ethnic health disparities through biomedical research generally and complex disease genetics specifically. The authors do not refer to self-reported race and/or ethnicity in the description of their IPF cohorts and remained (perhaps appropriately) focused on genetic ancestry of individuals in the performance of the quality control and statistical analysis of genetic data. That said, only 8% of individuals overall and 3% of individuals in the replication cohort were of non-European ancestry. The underlying prevalence of IPF across racial and/or ethnic groups is difficult to assess; however, in contrast to the 8% of non-White participants in the current study, an examination of 37 worldwide IPF clinical trial and registry studies demonstrated a heterogeneous estimate of 14% (range, 3–32%) of all participants being non-White (9). Moreover, only 23 of the 37 studies reported race or ethnicity, which is important to ensure diversity. A 2006 retrospective cohort study of 2,635 patients with IPF listed for lung transplantation reported that the 18% of non-White individuals had more severe IPF at transplant listing and worse post-transplant survival, suggesting that non-White individuals are underrepresented in IPF lung transplant and the proportion of non-White individuals with IPF may be even higher than 18% (10). Despite the small percentage of individuals of non-European ancestry with IPF in the manuscript by Zhang and colleagues, the authors have disrupted a paradigm by including these individuals in the overall analysis of deleterious *KIF15* variants associated with IPF. Citing possible bias due to population substructure (a legitimate concern in genetic association studies), most prior IPF genetic studies have exclusively analyzed individuals of European ancestry (2, 3, 11, 12). In addition to the social imperative to incorporate more population diversity in IPF genetics research, population differences in rare deleterious variants can augment discovery of disease-associated genes when multiple ancestry groups are analyzed (13). Thus, Zhang and colleagues may not have discovered IPF-associated rare deleterious variants in KIF15 if they had limited their study to a single ancestry group. Analyzing multiple ancestries can also augment statistical power for common genetic variant studies. For instance, Putman and colleagues studied the association of the common *MUC5B* promoter polymorphism (rs35705950) with subpleural interstitial lung abnormalities in the COPD Genetic Epidemiology (COPDGene) study and noted a similar point estimate for the odds ratio in non-Hispanic White and African American individuals despite a large difference in allele frequency (non-Hispanic White, 11%; African American, 2%) between the two populations (14).

We should celebrate the opportunity that Zhang and colleagues have given us to investigate *KIF15* as a novel pathologic mechanism for IPF independent of telomerase pathways. At the same time, we as a pulmonary community should strive to include more diverse populations in future clinical, epidemiologic, and genetic studies of IPF to improve health disparities and simultaneously increase the statistical rigor and generalizability of our research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Brian D. Hobbs, M.D., M.M.Sc.
Channing Division of Network Medicine

and

Division of Pulmonary and Critical Care Medicine
Brigham and Women's Hospital
Boston, Massachusetts

and

Harvard Medical School
Boston, Massachusetts

ORCID ID: 0000-0001-9564-0745 (B.D.H.).

References

1. King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. *PLoS Genet* 2019;15:e1008489.
2. 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;45:613–620.
3. Allen RJ, Guillen-Guio B, Oldham JM, Ma SF, Dressen A, Paynton ML, *et al.* Genome-wide association study of susceptibility to idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2020;201:564–574.
4. Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, *et al.* An exome sequencing study to assess the role of rare genetic variation in pulmonary fibrosis. *Am J Respir Crit Care Med* 2017;196: 82–93.
5. Armanios MY, Chen JJ, Cogan JD, Alder JK, Ingersoll RG, Markin C, *et al.* Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl J Med* 2007;356:1317–1326.
6. Nogee LM, Dunbar AE III, Wert SE, Askin F, Hamvas A, Whitsett JA. A mutation in the surfactant protein C gene associated with familial interstitial lung disease. *N Engl J Med* 2001;344:573–579.
7. Zhang D, Povysil G, Kobeissy PH, Li Q, Wang B, Amelotte M, *et al.* Rare and common variants in *KIF15* contribute to genetic risk of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2022;206:56–69.
8. Tanenbaum ME, Macůrek L, Janssen A, Geers EF, Alvarez-Fernández M, Medema RH. Kif15 cooperates with eg5 to promote bipolar spindle assembly. *Curr Biol* 2009;19:1703–1711.
9. Jalbert AC, Siafa L, Ramanakumar AV, Assayag D. Gender and racial equity in clinical research for idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Eur Respir J* 2022;59:2102969.
10. Lederer DJ, Arcasoy SM, Barr RG, Wilt JS, Bagiella E, D'Ovidio F, *et al.* Racial and ethnic disparities in idiopathic pulmonary fibrosis: a UNOS/OPTN database analysis. *Am J Transplant* 2006;6:2436–2442.
11. Fingerlin TE, Zhang W, Yang IV, Ainsworth HC, Russell PH, Blumhagen RZ, *et al.* Genome-wide imputation study identifies novel HLA locus for pulmonary fibrosis and potential role for auto-immunity in fibrotic idiopathic interstitial pneumonia. *BMC Genet* 2016;17:74.
12. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, *et al.* Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. *Lancet Respir Med* 2017;5:869–880.
13. Edenberg HJ, McClintick JN. Alcohol dehydrogenases, aldehyde dehydrogenases, and alcohol use disorders: a critical review. *Alcohol Clin Exp Res* 2018;42:2281–2297.
14. Putman RK, Gudmundsson G, Araki T, Nishino M, Sigurdsson S, Gudmundsson EF, *et al.* The *MUC5B* promoter polymorphism is associated with specific interstitial lung abnormality subtypes. *Eur Respir J* 2017;50:1700537.