Taking the "I" out of IPF

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This issue of the *European Respiratory Journal* contains a comprehensive review by Kropski *et al.* [1] that supports a genetic basis for idiopathic pulmonary fibrosis (IPF) and encourages us to think differently about this perplexing disease.

As the authors describe, the initial evidence that pulmonary fibrosis may have a genetic basis emerged from case reports and case series that reported multiple cases of idiopathic interstitial pneumonias (IIPs) clustering in families [2-6]. The epidemiology indicates that within families containing two or more cases of IIP (familial interstitial pneumonia) the development of familial interstitial pneumonia is associated with older age, male sex and ever having smoked cigarettes [6, 7]. The transmission pattern of inheritance is consistent with an autosomal dominant pattern, and 45% of the families demonstrated several subtypes of IIP within the same family, suggesting that IIP subtypes may be aetiologically related [6].

Initial family-based studies indicated that rare variants in surfactant protein genes (*SFTPA2* and *SFTPC*) [8-10] and telomerase related genes (*hTERT* and *TERC*) [11, 12] are associated with the development of familial interstitial pneumonia [8, 10, 13-17]. Rare variants of the telomerase genes were also found to be associated with the more common presentation of sporadic cases of IPF [11]. Through linkage and association, we identified a promoter variant (rs35705950) in the Mucin 5B (*MUC5B*) gene that is strongly associated with both familial and sporadic IPF [18]. The *MUC5B* promoter variant's association with IPF has been validated in seven subsequent independent cohorts [19-24], including our recent genome-wide association study (odds ratio for T (minor) allele=4.51, 95% CI 3.91–5.21; p=7.21×10^{-95}) [25]. The *MUC5B* promoter variant rs35705950 is present in ~50% of individuals with IPF and is recognised as the strongest known risk factor (genetic and otherwise) for the development of familial and sporadic forms of IPF. Subsequent genome-wide association studies have identified numerous additional loci associated with IPF, including *TERC* (3q26), *FAM13A* (4p22), *TERT* (5p15), *DSP* (6p24), *OBFC1* (10q24), *ATP11A* (13q34), *DPP9* (19p13), chromosomal regions 7p22 and 15q14-15, *TOLLIP* (11p15), and *SPPL2C* (17q21) [21, 25].

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Although these rare and common variants enhance the risk of developing IPF, none of them have proven causal. This suggests that the causal variants in these genes and loci have yet to be identified, or that the development of IPF is complex involving multiple gene variants or gene–environment interactions, or that false positive associations have been reported between these genetic variants and IPF. The hypothesis raised by Kʀᴏᴘsᴋɪ *et al.* [1], that rare variants are more penetrant than common variants and less interactive with environmental risks is both logical and provocative. However, the relationship between gene variants (rare or common) and the development of IPF is in need of further investigation, and will be informed substantially by whole genome sequencing in large numbers of families with familial interstitial pneumonia or even larger numbers of patients with sporadic IPF. An emerging vision is that these findings will lead to a greater understanding of disease aetiology and pathogenesis, and will result in novel interventions that substantially alter the clinical course of IPF.

Although the genetic variants have contributed significantly to our collective understanding of the aetiology of IPF, these findings have not yet clarified the pathogenesis of this disease. The gene variants and loci associated with the development of IPF point to alterations in host defence, DNA repair and cell senescence, and epithelial barrier function in the lung. More importantly, the genetic variants associated with IPF may be useful in identifying the disease earlier when less lung tissue has been destroyed [26]. However, the value of intervention in early forms of IPF needs further consideration. There is probably a more complicated relationship between inherited genetic variants and environmental factors that leads to the phenotype we identify as IPF. Therefore, while genotyping rare and common variants is an important part of ongoing translational and clinical research, the clinical implications of IPF risk genotypes need further definition to be useful in the general population. But given the potential benefits of an early diagnosis, it is reasonable to consider the role of genetic screening in first-degree relatives of patients with IPF and within families with familial interstitial pneumonia.

As Kʀᴏᴘsᴋɪ *et al.* [1] discuss in their review, the *MUC5B* promoter variant that confers greatest risk of disease [18-25] and is associated with higher expression of *MUC5B* in the human lung [18] is also associated with improved survival in IPF patients [18]. Other studies illustrate similar significant prognostic implications for variants in the *TOLLIP* [21] and *TLR3* [27] genes. The association between the *MUC5B* promoter variant and less progressive restrictive lung function in patients with IPF further highlights the prognostic relevance of these gene variants in IPF [20]. While these findings indicate that gene variants identify different subtypes of IPF that are prognostically distinct, these findings also support the notion that gene variants may prove important clinically and therapeutically. However, in the case of the *MUC5B* promoter variant there is another intriguing possibility to consider. A microbiome study in patients with IPF [28] and a basic study in genetically engineered mice [29] suggest that MUC5B may be an important component of lung host defence and that more MUC5B in the airspace enhances host defence in the lung. Thus, although the *MUC5B* promoter variant may enhance the risk of IPF, the associated enhanced expression of MUC5B may in fact select for individuals with robust airway host defence. This is also supported by the broad range of minor allele frequencies of rs35705950 in

Africans (0%), Asians (0%), Hispanics (2.3%), African Americans (3.3%) and Europeans (10%) (www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=35705950). The role of *MUC5B* in airway host defence also raises the possibility that the rs35705950 allele was under positive selective pressure among Europeans and retained at a relatively high frequency due to the selective advantage in airway immunity.

Further research into the clinical implications of genetic variants and IPF is particularly salient as new therapeutic options become available for patients; if different genetic risk variants confer different prognoses and perhaps different molecular mechanisms of disease, it would follow that therapeutic efficacy could vary as well. Although two new therapies (pirfenidone and nintedanib) have recently been approved in the USA for treatment of IPF, neither drug is curative and both drugs have modest effects on disease progression (125.3 mL and 193 mL lower mean annual rate of change in forced vital capacity for nintedanib and pirfenidone, respectively) [30, 31]. It remains possible that differential distribution of the *TOLLIP, TLR3* or *MUC5B* promoter variants in the intervention or placebo group accounted for the observed improvement with nintedanib or pirfenidone, or even the negative results seen in trials of other agents that are now considered ineffective in IPF [32-34]. To date, no studies have evaluated the effect of different risk variants and their potential effects on lung transplantation outcomes. The history of IPF clinical research reveals examples of drug trials with discordant findings when the trials were repeated [30, 35]. Such observations suggest the possibility that in different patient populations, presumably with different genetic risk factors, different therapies might be more effective. More importantly, clinical trials should control for the presence of prognosis-modifying genetic variants, since progression-free survival is a frequent primary end-point in IPF clinical trials [36, 37]. As evidence mounts that genetic risk influences disease progression, failure to control for such baseline patient characteristics would be akin to performing clinical trials in progressive chronic lung diseases that do not control for other traditionally recognised clinical factors like age, smoking status or baseline lung function.

For decades, IPF has remained an enigma, but the strength of the data linking inherited factors to development of disease suggests that "idiopathic pulmonary fibrosis" is a misnomer. As Kropski *et al.* [1] suggest, future studies will elucidate the molecular pathways leading to the phenotype of pulmonary fibrosis. These insights will assist investigators in creating more appropriate classifications and nomenclature for a decreasingly mysterious disease. More importantly, understanding the genetic causes of IPF will result in earlier disease recognition, novel interventions aimed at secondary prevention, and personalised approaches to halt the progression of established disease. As we begin to understand the genetic origins of this disease, we need to reconsider the wisdom of the nomenclature we use to describe IPF.

Acknowledgments

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