Genetics of Interstitial Lung Disease: *Vol de Nuit* (Night Flight)

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ABSTRACT: Interstitial lung disease (ILD) is a chronic, progressive fibrotic lung disease with a dismal prognosis. ILD of unknown etiology is referred to as idiopathic interstitial pneumonia (IIP), which is sporadic in the majority of cases. ILD is frequently accompanied by rheumatoid arthritis (RA), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), and other autoimmune diseases, and is referred to as collagen vascular disease-associated ILD (CVD-ILD). Susceptibility to ILD is influenced by genetic and environmental factors. Recent advances in radiographic imaging techniques such as high-resolution computed tomography (CT) scanning as well as high-throughput genomic analyses have provided insights into the genetics of ILD. These studies have repeatedly revealed an association between IIP (sporadic and familial) and a single nucleotide polymorphism (SNP) in the promoter region of the mucin 5B (*MUC5B*). *HLA-DRB1*11* alleles have been reported to correlate with ILD in European patients with SSc, whereas in Japanese patients with RA, the HLA-DR2 serological group was identified. The aim of this review is to describe the genetic background of sporadic IIP, CVD-ILD, drug-induced-ILD (DI-ILD), pneumoconiosis, and hypersensitivity pneumonitis. The genetics of ILD is still in progress. However, this information will enhance the understanding of the pathogenesis of ILD and aid the identification of novel therapeutic targets for personalized medicine in future.

KEYWORDS: interstitial lung disease, idiopathic interstitial pneumonia, collagen vascular disease-associated interstitial lung disease, human leukocyte antigen, *MUC5B*

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Introduction

Interstitial lung disease (ILD) is a chronic, progressive fibrotic lung disease with a dismal prognosis. Symptoms of ILD are a non-productive cough and dyspnea, and clinical examinations are characterized by hypoxemia and a reduced diffusing capacity of the lung for carbon monoxide. Computed tomography (CT) scans reveal ground-glass attenuation patterns, irregular linear opacities, and honeycombing. ILD is classified as idiopathic interstitial pneumonia (IIP), collagen vascular disease-associated ILD (CVD-ILD), drug-induced-ILD (DI-ILD), pneumoconiosis, and hypersensitivity pneumonitis. IIP is ILD of unknown etiology. Familial IIP is defined by the presence of confirmed IIP in two or more members of the same family; it is estimated that 0.5–2% of IIP cases are familial.[1] This suggests that genetic factors influence the pathogenesis of IIP. ILD is frequently associated with rheumatoid arthritis (RA), systemic sclerosis (SSc), and polymyositis/dermatomyositis (PM/DM), as well as other autoimmune diseases, and is classified as CVD-ILD. DI-ILD is caused by the use of anticancer or disease-modifying anti-rheumatic drugs, including bleomycin, gefitinib, gold sodium thiomalate, and methotrexate.[2–5] It is believed that the Japanese have a higher susceptibility to DI-ILD than other ethnic groups,[6] suggesting that ethnic genetic differences are involved in the pathogenesis of

DI-ILD. Pneumoconiosis is caused by inhalation of the dust of carbon, asbestos, silica, or beryllium, while hypersensitivity pneumonia is triggered following inhalation of the dust of bacteria, fungi, insects, or animal antigens. Susceptibility to pneumoconiosis and hypersensitivity pneumonitis varies among individuals, indicating that genetic factors also play a role.[7] The pathogenesis of ILD is affected by a combination of genetic and environmental factors, such as smoking, microaspiration, or drugs, though all the heritability could not be explained by recent genome studies.[8]

IIP

IIP was first classified according to pathological findings, but it is also clinically defined as idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia, respiratory bronchiolitis-associated ILD, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, and acute interstitial pneumonia. IIP usually progresses chronically; sometimes acute exacerbation occurred.[9] IPF has a poor prognosis, and it is characterized by usual interstitial pneumonia (UIP) on CT images, with evidence of irregular linear opacities and honeycombing. In NSIP, CT images reveal bilateral ground-glass attenuation patterns, predominantly in the subpleural and basal regions. Because NSIP is frequently accompanied by autoimmune disease, in particular SSc, it is thought to be one of the manifestations of lung-dominant connective tissue disease or undifferentiated connective tissue disease.[10–12] Autoimmune disease-specific symptoms and/or autoantibodies are present in patients with NSIP, but these findings are insufficient for a definitive diagnosis of autoimmune disease.

Genetic association studies have been intensively conducted in IPF. The candidate gene approach was performed to identify causative genes based on the limited knowledge of IPF pathogenesis. Genes implicated in inflammation, cell growth, cell death, proteins secreted from alveolar epithelial cells, and causative genes of familial ILD under Mendelian inheritance were candidates, including human leukocyte antigen (*HLA*), tumor necrosis factor-α (*TNF-α*), transforming growth factor-β1 (*TGFB1*), surfactant protein C (*SFTPC*), telomerase reverse transcriptase (*TERT*), and telomerase RNA component (*TERC*).

HLA molecules present intracellular or extracellular antigens to T-cell receptors, resulting in T-cell activation. *HLA* alleles are associated with many types of immunological disorder. Higher frequencies of the *HLA-B15* and the *HLA-DR2* (*DRB1*15:01*) alleles were reported in IPF.[13–15] A recent study of a Mexican population suggested that IPF is associated with major histocompatibility complex class I-related chain A (MICA).[16] TNF-α is one of the proinflammatory cytokines implicated in the pathogenesis of IPF. Although the *TNF* gene is located in the *HLA* region, the homozygous -308 allele is more frequent in IPF patients.[17] TGF-β1 is a growth factor that promotes fibroblast proliferation and collagen synthesis. The R25P *TGFB1* polymorphism affects disease progression in sporadic IPF.[18] Pulmonary surfactant is a lipoprotein complex that is crucial for the maintenance of lung alveolar structure, and it consists of surfactant proteins A, B, C, and D. Mutated *SFTPC* with gain-of-function causes endoplasmic reticulum stress, leading to the death of alveolar epithelial cells. The telomerase complex, which is encoded in part by *TERT* and *TERC*; the DNA helicase encoded by *RTEL1*; and OB fold-containing protein 1 (*OBFC1*) regulate telomere length and cell survival. *TERT*, *TERC*, and *RTEL1* mutations with loss-of-function cause dyskeratosis congenita, which is characterized by skin hyperpigmentation, nail dystrophy, and ILD.[19,20] In patients with familial IPF, mutations in the *SFTPC*, *SFTPA2*, *TERT*, and *TERC* genes have been documented. (Precise descriptions of familial ILD are available in another review article by Kitazawa et al in this supplement.).[21–23] With respect to sporadic IPF, the $6A^4$ allele of *SFTPA1* was identified in non-smokers, while the 1580C allele of *SFTPB* was associated with smokers.[24] Mutations in genes associated with familial ILD were rarely observed in sporadic IPF.[25] Thus, studies using the candidate gene approach have enabled the identification of several causative genes for sporadic IPF.

Genome-wide linkage analysis revealed a link between familial IPF and a region in chromosome 4 encoding the ELMO/CED-12 domain containing 2 (*ELMOD2*), a gene that is involved in apoptosis.[26] Another genome-wide linkage study identified a single nucleotide polymorphism (SNP) in the promoter region of the mucin 5B (*MUC5B*) gene as a risk allele for both familial and sporadic IPF.[27,28] This association between IPF and the minor allele (T) of the *MUC5B* SNP rs35705950 was confirmed in some Asian populations,[29–31] although the frequency of this allele was lower than in Caucasians. However, the rs35705950 SNP was not associated with ILD in SSc patients,[32] suggesting differences in the mechanism of disease pathogenesis. Another insertion/deletion polymorphism in the *MUC5B* gene is associated with diffuse panbronchiolitis.[33] MUC5B is one of the two major secretory mucins and is mainly expressed by submucosal gland cells in the lung. The T allele of rs35705950 upregulates *MUC5B* expression in the lung, and an excess of secreted MUC5B protein may interfere with the mechanisms of alveolar repair. Surprisingly, the risk allele in *MUC5B* was associated with an improved survival in IPF.[34] This indicates that the *MUC5B* SNP may be less important in severe forms of IPFs compared with milder IPF. Recent genome-wide association studies (GWAS) revealed the association of several genes with sporadic IPF, including *MUC5B*, *TOLLIP*, *TERT*, *SPPL2C*, and *OBFC1*.[35–37] *TOLLIP* encodes an adaptor protein that regulates the intracellular degradation of TGF-β type 1 receptor. *SPPL2C* encodes a signal peptide peptidase that is required for intra-membrane proteolysis. Signal peptide peptidases are implicated in immune system regulation, cleaving signal peptides from HLA class I molecules that are subsequently

presented by HLA-E, a non-classical HLA with high expression levels in the lung.[38,39] These genetic studies will provide clues toward a better understanding of the pathogenesis of IPF.

CVD-ILD

RA-associated ILD (RA-ILD). RA is a chronic, systemic inflammatory disease that mainly affects the joints, causing pain, bone erosion, disability, and reduced survival, and it is often complicated by the presence of extra-articular manifestations, including ILD. Recent studies have led to the identification of many susceptibility genes for RA, including *HLA-DRB1*, *STAT4*, *TNFAIP3*, *CCR6*, *CTLA4*, *BLK*, *IRF5*, *PTPN22*, *ARID5B*, *ANKRD55*, *NFKBIE*, and *PADI4*.[40] It is estimated that one-third to one-half of the genetic influence on RA susceptibility is accounted for by *HLA-DRB1*.[41] *HLA* is known to be associated with RA. Some *HLA-DR* alleles correlate with RA susceptibility.[42] A conserved amino acid sequence at positions 70–74 (QKRAA, RRRAA, or QRRAA) of the HLA-DRβ chain is known as a shared epitope (SE), because it is found in almost all the RA-associated *HLA-DR* alleles.[42]

The presence of anti-citrullinated peptide antibodies (ACPA) has higher specificity as a marker of RA than rheumatoid factor. Thus, ACPA is thought to play a role in the pathogenesis of RA, in particular, because SE alleles are strongly associated with ACPA-positive RA, but relatively weakly associated with ACPA-negative RA.[43,44] Several studies have found that *DRB1*04:01* and *DRB1*04:05*, both SE alleles, display the strongest association with RA in European and East Asian populations, respectively.[42]

ILD frequently co-occurs with RA. Although NSIP is predominant in CVD-ILD, UIP is observed in a considerable proportion of RA-ILD cases.[45] ILD in RA is one of the extra-articular manifestations and influences RA prognosis.[46] A study reported that median survival after diagnosis of RA-ILD was three years.[47] DR2 alleles (*DRB1*15* and *DRB1*16*) were associated with ILD in a Japanese RA population.[48–50] It was reported that SEs had a clear protective effect for ILD in RA,[49] although in other studies, a weak protective effect was noted.[48,50,51] ACPA are observed in smoking patients with ILD alone.[52,53] The presence of citrullinated peptides in the lung of RA-ILD patients is thought to be smoking related,[54] and it appears that autoantigens contribute to the pathogenesis of RA and RA-ILD.[55] *DRB1*04:05* is strongly associated with ACPA, although these alleles were negatively associated with ILD in RA. Although the implication of this finding is not clear, it may suggest that SEs are not involved in RA complicated with ILD. Many GWAS have been performed in RA; however, a few have been validated in RA-ILD subpopulations. To date, targeted association studies of the *MUC5B* SNP with RA-ILD have not been published.

SSc-associated ILD (SSc-ILD). SSc is a complex autoimmune disorder of unknown etiology and is characterized by fibrosis of the skin and internal organs, including ILD, small vessel vasculopathy, and the production of anti-nuclear antibodies. Reported genetic risk factors for SSc were *HLA-DRB1*, *DQB1*, *DPB1*, *DPB2*, *IRF5*, *STAT4*, *CD247*, *CDH7*, *IRF4*, and others.[56–58] Increased or decreased frequencies of *HLA* alleles correlate with SSc. Different *HLA* class II alleles are associated with SSc susceptibility, according to the ethnic group: *HLA-DRB1*11:04*, *DQB1*03:01*, and *DQB1*26 epi* (*DQB1* alleles with residues other than leucine at position 26) in Europeans[59,60] and *DRB1*15:02* and *DQB1*05:01* in Asians.[61–65]

Patients with SSc display several specific autoantibodies, anti-centromere antibodies (ACA),[66] and anti-topoisomerase antibodies (ATA; also termed Scl-70).[67] ACA are observed in a subset of patients with limited cutaneous SSc, which is characterized by skin thickening restricted to the fingers and hands and less severe internal organ involvement. ATA occur in patients with diffuse cutaneous SSc, with extensive and progressive skin lesions, and serious internal organ involvement, including ILD, is manifested.

ILD, predominantly NSIP, is a common complication of SSc, and it confers a poor prognosis.[68–70] It is necessary to clarify the pathogenesis of ILD as a complication of SSc. There is still limited information on the associations of *HLA* with SSc-ILD. *HLA-B*62*, *C*06*, and *DRB1*11* were associated with ILD in European and African SSc patients,[71–73] while *DPB1*03:01* and DR51 were associated with ILD in Asian SSc patients.[74,75] DR51 (*DRB5*01* and *DRB5*02*) alleles are unique to individuals with DR2 alleles, because the *DRB5* locus only exists in haplotypes possessing DR2 alleles of the *DRB1* locus. Therefore, DR2 may be related to ILD in Asian patients with SSc.

Other non-*HLA* genes have also been associated with SSc-ILD. Using the candidate gene approach, polymorphisms in *CD226*, *MMP12*, *SFTPB*, *CTGF*, *HGF*, *IRAK1*, and *TCRBV* were detected in SSc-ILD.[76–84] An SNP in *IRF5* is known to be associated with longer survival and milder form of ILD in patients with SSc.[85] However, the SNP rs35705950 in the promoter region of *MUC5B* gene, which is associated with IPF,[27] was not identified as a risk factor in SSc-ILD patients.[32] Except for *HLA*, no other IPF-related polymorphisms have been associated with SSc-ILD. This may be explained by the finding that NSIP is predominant in SSc-ILD, reflecting the different pathogenesis of IPF compared with SSc-ILD.

PM/DM-associated ILD (PM/DM-ILD). PM and DM are idiopathic myopathies characterized by inflammation of the skeletal muscle as well as extramuscular manifestations, including ILD, skin rashes, malignancy, and the production of specific autoantibodies. Genetic risk factors for PM/DM include alleles of the loci *HLA-DRB1*, *PLCL1*, *BLK*, *CCL21*, *TYK2*, *STAT4*, and others.[86–88] Different *HLA* class II alleles are associated with PM/DM susceptibility, according to ethnicity: *HLA-DRB1*03* in Europeans[89] and *DRB1*08:03* in Asians.[90]

Table 1. Susceptibility genes of ILD.

		SUSCEPTIBILITY GENES	REFERENCES
IPF	Familial	*SFTPA2, SFTPC, TERT, TERC, RTEL1*	19–22
		ELMOD2, MUC5B	26, 27
	Sporadic	HLA-B15, *DRB1*15:01, MICA*	13–16
		TNF, TGFB1, SFTPA1, SFTPB	17, 18, 24, 25
		TOLLIP, TERT, SPPL2C, MUC5B	27–29, 35–37
CVD-ILD	RA-ILD	*DRB1*16:02, DRB1*15:02*	48–50
	SSc-ILD	*HLA-B*62, HLA-C*06, DRB1*11*	71–73
		*DPB1*03:01*, DR51	74, 75
		CD226, MMP12, SFTPB, CTGF,	76–85
		HGF, IRAK1, TCRBV, IRF5	
	PM/DM-ILD	*DRB1*03, DRB1*01:01, DRB1*04:05*	94, 95
DI-ILD		*HLA-A*31:01*	113
Pneumoconiosis		HLA-B54, *TNF, IL1RN, MUC5B, HLA-DPB1*	119–121, 7
Hypersensitivity pneumonitis		HLA-DR3, HLA-DQ3	122, 123

Abbreviations: ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; CVD-ILD, collagen vascular disease-associated ILD; DI-ILD, drug-induced-ILD; RA-ILD, rheumatoid arthritis-associated ILD; SSc-ILD, systemic sclerosis-associated ILD; PM/DM-ILD, polymyositis/dermatomyositis-associated ILD.

Several specific autoantibodies are detected in PM/DM, in particular, anti-aminoacyl-transfer RNA synthetase (ARS) antibodies, including anti-Jo-1 antibodies, and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies. Anti-ARS antibodies are associated with chronic ILD.[91] Anti-MDA5 antibodies are observed in acute-onset diffuse ILD occurring in clinically amyopathic DM and confer a poor prognosis.[92,93] The association of *HLA-DRB1*03* with the presence of anti-ARS antibodies or chronic ILD in PM/DM was reported.[94] Frequencies of *DRB1*01:01* or *DRB1*04:05* were higher in Japanese DM patients with anti-MDA5 antibodies.[95] Thus, the genetic factors that influence susceptibility to CVD-ILD are not same as those for IIP.

DI-ILD

DI-ILD may occur in patients treated with anti-cancer drugs,[3,96] RA patients treated with disease-modifying anti-rheumatic drugs,[4,5,97] hepatitis patients treated with interferons or Chinese herbal drugs, and patients with infectious diseases treated with antibiotics. DI-ILD occurs with acute onset and progression within a month, and is accompanied with clinical symptoms of fever, non-productive cough, or shortness of breath, and findings of fine crackle or radiologic evidence of diffuse ILD. Risk factors for DI-ILD in patients with cancer include pre-existing ILD, male sex, smoking, poor functional status, concomitant radiation therapy, no history of chemotherapy, and hypoalbuminemia.[3] Risk factors for DI-ILD in RA are pre-existing RA-ILD, older age, diabetes, previous use of disease-modifying anti-rheumatic drugs, and hypoalbuminemia.[5] It is thought that Japanese are more susceptible to DI-ILD than other ethnic groups.[6] This information suggests the presence of genetic factors involved in the pathogenesis of DI-ILD. The prognosis for patients with DI-ILD is quite poor. It is important to analyze the pathogenesis of DI-ILD and to predict and prevent DI-ILD.

A striking association between drug- and ethnicity-specific *HLA* alleles and cutaneous adverse reactions has been shown for allopurinol (*B*58:01*),[98] abacavir (*B*57:01*),[99,100] carbamazepine (*B*15:02* for Chinese, *A*31:01* for Japanese and Europeans),[101–103] and methazolamide (*B*59:01* for Japanese).[104] In addition, other studies have focused on the association of *HLA* alleles and drug-induced hypersensitivity reactions, including agranulocytosis (*DRB1*08:03*: methimazole),[105] drug-induced liver injury (*A*33:03*: ticlopidine, tiopronin; *B*57:01*: flucloxacillin; *DRB1*15:01*: amoxicillin–clavulanate),[106–109] drug-induced myopathy (*DRB1*11:01*: statin),[110] and drug-induced proteinuria (DR3: D-penicillamine, gold salts, *DRB1*08:02*: bucillamine).[111,112] Similarly, *HLA-A*31:01* was associated with an increased risk of DI-ILD in methotrexate-treated Japanese RA patients.[113] In contrast, no genetic association was detected with DI-ILD in Japanese patients with non-small-cell lung cancer receiving gefitinib,[114] though the sample size of the study does not seem enough. The molecular mechanisms of drug hypersensitivity related to certain *HLA* alleles are not clear. The complex of HLA molecules with drugs might directly activate T cells.[115] Drugs or their metabolites might work as haptens and bind to peptides preloaded on the HLA molecules. Drugs might bind to the specific allele, producing alterations in the repertoire of presented self-peptides.[116] These observations imply that *HLA* plays a substantial role in drug-induced hypersensitivity reactions such as DI-ILD. They may provide information for clinical appreciation to predict DI-ILD, forwarding personalized medicine.

Pneumoconiosis and Hypersensitivity Pneumonitis

Inhalation of inorganic dust causes pneumoconiosis, an occupational lung disease, whereas inhalation of organic dust causes hypersensitivity pneumonitis. The clinical features are heterogeneous, and they progress acutely or chronically. In addition, silica exposure may also lead to the development of various autoimmune diseases.[117] RA with pneumoconiosis following silica exposure is called Caplan's syndrome.[118] Results from genetic association studies on pneumoconiosis indicate that the HLA-B54 allele is associated with silicosis in Japanese patients.[119] Because *DRB1*04:05* is the dominant SE allele in the Japanese RA population, the *HLA-B*54:01-DRB1*04:05* haplotype underlies the susceptibility of this ethnic group to Caplan's syndrome. Associations of SNPs in *TNF* and *IL1RN* with silicosis were also reported.[120] The SNP rs2672794 in the promoter region of the *MUC5B* gene, which is different from the SNP associated with IPF,[27] is associated with coal workers' pneumoconiosis in Chinese populations.[7] *HLA-DPB1* alleles encoding a glutamic acid residue at position 69 are associated with chronic beryllium lung disease.[121] HLA-DR3 alleles are associated with pigeon breeder's lung.[122] HLA-DQ3 alleles are associated with Japanese summer-type hypersensitivity pneumonitis induced by *Trichosporon cutaneum*.[123] Thus, several genetic factors are known to be involved in pneumoconiosis and hypersensitivity pneumonitis.

Conclusion

Because ILD confers a dismal prognosis on patients, it is paramount to elucidate the pathogenesis of ILD. Genetic studies of ILD have been advanced using improved methods – greater sample sizes, higher numbers of polymorphisms genotyped by the array method, and focused studies on population or disease subsets. Many findings were obtained from these optimized genetic studies. Nevertheless, mechanisms that remain unknown are involved in the pathogenesis of ILD. It is imperative to study ILD using pioneering genetic research technology, for example, genotyping of rare variants with next-generation sequencing, investigation of gene–gene and gene–environment interactions, and epigenetic analysis of blood and lung tissues. These novel approaches may yield useful information for the development of effective and specific therapies for ILD, ushering in a new era of ILD treatment. After a long night flight (*Vol de Nuit*) over glimmerings, the genetics of ILD are eventually facing the first gray light of dawn. Thus, genetics of ILD is still in progress, and the clinical appreciation of the results is expected in future.

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Author Contributions

Conceived and designed the experiments: HF, SO, KS, NT, ST. Analyzed the data: HF, SO. Wrote the first draft of the manuscript: HF. Contributed to the writing of the manuscript: HF, SO, KS, NT, ST. Agree with manuscript results and conclusions: HF, SO, KS, NT, ST. Jointly developed the structure and arguments for the paper: HF, SO, KS, NT, ST. Made critical revisions and approved final version: HF, SO, KS, NT, ST. All authors reviewed and approved of the final manuscript.

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