Introductions

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 accounts for 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

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

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Supplementary Issue: Current Developments in Interstitial Lung Disease

**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 accounts for 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.

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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. The pathogenesis of ILD is affected by a combination of genetic and environmental factors, such as smoking, micro-aspiration, or drugs, though all the heritability could not be explained by recent genome studies.

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. IPF usually progresses chronically; sometimes acute exacerbation occurred. 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. 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 mechanism of disease pathogenesis. Another insertion/deletion polymorphism in the MUC5B gene is associated with diffuse panbronchiolitis. 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 mucins and is mainly expressed by submucosal gland cells.

Surprisingly, the risk allele in TOLLIP, a type 1 receptor. This association between IPF and the minor allele (T) of the MUC5B SNP rs35705950 was confirmed in some Asian populations, although the frequency of this allele was lower than in Caucasians. However, the rs35705950 SNP was not associated with ILD in SSC patients, suggesting differences in the mechanism of disease pathogenesis. Another insertion/deletion polymorphism in the MUC5B gene is associated with diffuse panbronchiolitis. 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. 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. 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 degraded. The R25P TGFB1 polymorphism affects disease progression in sporadic IPF. 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. In patients with familial IPF, mutations in the SFTP C, 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.) With respect to sporadic IPF, the 6A allele of SFT P A1 was identified in non-smokers, while the 1580C allele of SFTP B was associated with smokers. Mutations in genes associated with familial ILD were rarely observed in sporadic IPF. 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. 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. This association between IPF and the minor allele (T) of the MUC5B SNP rs35705950 was confirmed in some Asian populations, although the frequency of this allele was lower than in Caucasians. However, the rs35705950 SNP was not associated with ILD in SSC patients, suggesting differences in the mechanism of disease pathogenesis. Another insertion/deletion polymorphism in the MUC5B gene is associated with diffuse panbronchiolitis. 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. 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. 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 degraded. The R25P TGFB1 polymorphism affects disease progression in sporadic IPF. 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. In patients with familial IPF, mutations in the SFTP C, 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.) With respect to sporadic IPF, the 6A allele of SFT P A1 was identified in non-smokers, while the 1580C allele of SFTP B was associated with smokers. Mutations in genes associated with familial ILD were rarely observed in sporadic IPF. Thus, studies using the candidate gene approach have enabled the identification of several causative genes for sporadic IPF.

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Presented by HLA-E, a non-classical HLA with high expression levels in the lung. 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. It is estimated that one-third to one-half of the genetic influence on RA susceptibility is accounted for by HLA-DRB1. HLA is known to be associated with RA. Some HLA-DR alleles correlate with RA susceptibility. A conserved amino acid sequence at positions 70–74 (QKRAAQ, RRRRA, 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.

The presence of anti-citrullinated peptide antibodies (ACPAs) 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. 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.

ILD frequently co-occurs with RA. Although NSIP is predominant in CVD-ILD, UIP is observed in a considerable proportion of RA-ILD cases. ILD in RA is one of the extra-articular manifestations and influences RA prognosis. A study reported that median survival after diagnosis of RA-ILD was three years. DR2 alleles (DRB1*15 and DRB1*16) were associated with ILD in a Japanese RA population. It was reported that SEs had a clear protective effect for ILD in RA, although in other studies, a weak protective effect was noted.

ACPA are observed in smoking patients with ILD alone. The presence of citrullinated peptides in the lung of RA-ILD patients is thought to be smoking related, and it appears that autoantigens contribute to the pathogenesis of RA and RA-ILD. 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. 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 and DRB1*15:02 and DQB1*05:01 in Asians.

Patients with SSc display specific autoantibodies, anti-centromere antibodies (ACA), and anti-topoisomerase antibodies (ATA; also termed Scl-70). 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. 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, while DPB1*03:01 and DR51 were associated with ILD in Asian SSc patients. 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, HGFR, IRAK1, and TCRBV were detected in SSc-ILD. An SNP in IRF5 is known to be associated with longer survival and milder form of ILD in patients with SSc. However, the SNP rs35705950 in the promoter region of MUC5B gene, which is associated with IPF, was not identified as a risk factor in SSc-ILD patients. 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 other. Different HLA class II alleles are associated with PM/DM susceptibility, according to ethnicity: HLA-DRB1*03 in Europeans and DRB1*08:03 in Asians.
Several specific autoantibodies are detected in PM/DM, in particular, anti-aminocarboxyl-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: fluvoxacinil; DRB1*15:01: amoxicillin–clavulanate),106–109 drug-induced myopathy (DRB1*11:01: statin),110 and drug-induced proteinuria (DR3: ß-penicilamine, 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.
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Pneumoconiosis and Hypersensitivity Pneumonitis

Inhalation of inorganic dust causes pneumoconiosis, an occupa-
tional lung disease, whereas inhalation of organic dust causes
hypersensitivity pneumonitis. The clinical features are hetero-
genous, and they progress acutely or chronically. In addition,
silica exposure may also lead to the development of various auto-
mune 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*0405 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 syn-
drome. Associations of SNPs in TNF and ILIRN 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,22 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 Trichos-
pon 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 para-
mount 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 use-
ful 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
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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 the final
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