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Genetic susceptibility in pneumoconiosis☆

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Abstract

A large number of cellular mediators such as cytokines, antioxidants and growth factors have been implicated in the pathogenesis of chronic inflammatory and fibrotic diseases. Common functional polymorphisms in these genes have been shown to influence individual susceptibility to these diseases. Silicosis, coal worker pneumoconiosis, progressive massive fibrosis and berylliosis are examples of fibrotic pneumoconiosis and are characterized by irreversible fibrotic lesions in the lung resulting from chronic dust inhalation. Although the materials are the major contributory factors of the disease pathogenesis, not all individuals exposed to similar levels develop disease. This suggests that there is a genetic predisposition to their development. Therefore, an understanding of genetic variability and the interaction between genetic and environmental factors is crucial to the identification of high-risk individuals and prevention and treatment of these diseases.
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1. Introduction

In contrast to mutations, common allelic variants are present in high frequencies (>1%) in the general population. Among these variants, the most represented type of variations is single nucleotide substitutions, referred to as single nucleotide polymorphisms (SNPs). "Susceptibility profiles" reflecting the combined influence of multiple common risk alleles defines inter-individual variability due to genetics in the population. Common variants generally possess low or incomplete penetrance, interact with other genes or environment and consequently show low risk associations in epidemiological studies (e.g., odd ratios ∼ 1.5 – 2). Functional variants that affect phenotype are believed to contribute to the risk of common polygenic diseases, and this has led to the common disease-common variant (CD-CV) hypothesis. Several examples of well established associations between common variants and common diseases include APOE*E4 and Alzheimer's disease (Saunders et al., 1993), CCR5Δ32 and resistance to HIV infection (Dean et al., 1996) and α1-antitrypsin (AAT) deficiency and chronic obstructive pulmonary disease (COPD) (Poller et al., 1990).

Although genetic association studies help to uncover the contribution of genetic background in disease susceptibility and severity, complex interplay between genetic and environmental factors creates a challenge in understanding the etiology of complex diseases. Environmental epidemiology using genetic information has focused primarily on examining hypothesis-driven associations between environmental/occupational diseases and specific polymorphisms such as silicosis and

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TNFα-308 (Yucesoy et al., 2001b), chronic beryllium disease and HLA-DP Glu69 (Lombardi et al., 2001; McCanlies et al., 2004) in well characterized populations. Genetic modifiers are known for a number of common complex diseases where immune/inflammatory mediators and environmental factors play a role. This review summarizes the results of recent studies on the associations of common gene variants with pulmonary fibrosis, with a specific focus on occupationally exposed populations.

2. Genes involved in chronic inflammatory/fibrotic lung diseases

The pathogenesis of fibrotic lung diseases involve activation of inflammatory cells, fibroblast cell proliferation and the enhanced synthesis and/or breakdown of extracellular matrix components (Borm and Schins, 2001). Cytokines, chemokines, and growth factors play a crucial role in the onset, progression and termination of these reactions. Here, representative mediators whose genetic variants implicated in the development/progression or severity of fibrotic lung diseases are described.

The pathogenesis of pulmonary fibrosis appears to be driven by persistent inflammation where pro-inflammatory cytokines such as TNFα, IL-1 and IL-6 play a central role. TNFα was one of the earliest cytokine implicated in the pathogenesis of pulmonary fibrosis, as its over-expression promotes fibroblast proliferation and collagen deposition (Piguet et al., 1990). TNFα also promotes matrix-degrading gelatinases and fibroblast migration which result in matrix-remodeling (Selman et al., 2001). Increased amounts of TNFα were reported in the bronchoalveolar lavage fluid (BALF) of patients with idiopathic pulmonary fibrosis (IPF) or asbestosis (Zhang et al., 1993). It was also proposed that the measurement of coal dust-induced TNFα release (along with TGFβ) could be used as a marker of coal workers' pneumoconiosis (CWP) for the identification of high- and low-risk groups (Borm and Schins, 2001).

The IL-1 family (IL-1α, IL-1β and IL-1 receptor antagonist (RA)) has pro-inflammatory and fibrogenic effects providing a role in the initial fibrotic events. Both IL-1α and IL-1β induce fibroblasts to produce additional cytokines such as IL-6, and collagens (Raines et al., 1989). IL-1RA, a naturally occurring antagonist of the IL-1 receptor, can attenuate IL-1 signaling and help resolve inflammation after injury. Administration of IL-1RA decreases lung fibrosis in bleomycin and silica-induced fibrosis in mice (Piguet et al., 1993). Significantly increased levels of IL-1RA can be found in the BALF of patients with IPF and sarcoidosis (Rolfe et al., 1993; Smith et al., 1995).

IL-6, another pro-inflammatory cytokine, has been shown to help mediate interstitial lung diseases either alone or in concert with TNFα (Shahar et al., 1996). Over-expression of IL-6 is strongly associated with the development of fibrosis (Baecher-Allan and Barth, 1993; Yoshida et al., 1995). Furthermore, increased levels of IL-6 are found in BALF from patients with IPF (Takizawa et al., 1997).

TGFβ is the most widely studied cytokine in the context of fibrosis due to its pleiotropic activity on inflammatory/immune cells, structural cells, wound healing and tissue remodeling (Branton and Kopp, 1999; Wahl et al., 1989). Both experimental animal and human studies support the role of TGFβ in fibrosis. For example, TGFβ gene expression and protein production are increased in bleomycin, silica, asbestos, and radiation-induced pulmonary fibrosis in experimental animals (Liu et al., 1996; Phan and Kunkel, 1992; Rube et al., 2000; Williams et al., 1993). Increased TGFβ1 production has also been demonstrated in patients with IPF, sarcoidosis, pneumoconiosis, asbestosis, and radiation-induced fibrosis (Jagirdar et al., 1997; Khalil et al., 1996).

A number of other mediators have been implicated in the pathogenesis of fibrosis through the degradation and remodeling of ECM. Degradation of ECM is mediated primarily by metalloproteinases (MMPs) (Kuwano et al., 2001; Pardo and Selman, 2002). Disruption of the regulated balance between MMPs and tissue inhibitors of metalloproteinases (TIMPs) during normal tissue metabolism plays a crucial role in the formation of ECM and remodeling. (Fukuda et al., 1998; Pardo et al., 1992; Ramos et al., 2001; Selman et al., 2000). Increased expression of MMP-1, -2, -8 and -9 are found in experimental models of pulmonary fibrosis (Yaguchi et al., 1998) and in patients with IPF and sarcoidosis (Atkinson and Senior, 2003; Henry et al., 2002). There is also evidence implicating various pro-fibrotic factors, such as platelet derived growth factor (PDGF), macrophage chemotactic protein (MCP-1), insulin-like growth factor (IGF-1), macrophage inflammatory protein (MIP-1α), endothelin-1 (ET-1) and IL-8 in different stages of human and experimental pulmonary fibrosis.

Oxidative stress plays a major role in the pathogenesis of interstitial lung diseases affecting fibroblast proliferation, apoptosis and the cytokine microenvironment (Mastruzzo et al., 2002; Schins and Borm, 1999). Many chemical and physical agents in the environment, including mineral dusts are potent generators of reactive oxygen species (ROS). Antioxidant enzymes glutathione *S*-transferases (*GST*) and manganese superoxide

Table 1
Examples of associations between genetic variants and fibrotic lung diseases

Disease	Gene/variant	References
Chronic beryllium disease (CBD)	TNFα (-308); TGFβ1 (codon 25); ACE (in/del)	Gaede et al. (2005); Maier et al. (1999, 2001)
Coal workers' pneumoconiosis (CWP)	TNFα (-308)	Wang et al. (2005); Zhai et al. (1998)
Farmer's lung disease	TNFα (-308); CD14 (-159, 1619)	LeVan (2005); Schaaf et al. (2001)
Fibrosing alveolitis	IL-1RA (+2018); TNFα (-308)	Whyte et al. (2000)
Silicosis	TNFα (-238); IL-1RA (+2018) HLA-Bw54	Corbett et al. (2002); Honda et al. (1993); Yucesoy et al. (2001a, 2001b)

dismutase (*MnSOD*) are important components of lung defense against oxidative stress and polymorphisms exist in these genes may represent important disease modifiers.

Many of the previously discussed genes contain genetic variations in their regulatory regions that influence their expression level. Although recent evidence suggests their associations with common complex human diseases such as cardiovascular diseases, cancer, neurodegenerative diseases, the role of genetic polymorphisms in pulmonary fibrosis have been limited to several studies. Table 1 shows some examples of associations between genetic polymorphisms and fibrotic lung diseases. Only representative examples are presented here.

3. Genetic associations in pneumoconiotic diseases

Although many candidate genes are known to be involved in the pathogenesis of pulmonary fibrosis, only a limited number of their variants have been evaluated to date for associations. Most genetic association studies have focused on polymorphisms in the IL-1 and TNF gene families, however, chemokines, HLA and antioxidant gene variations have been examined to some extent.

3.1. Silicosis

Silicosis, an interstitial lung disease resulting from inhalation of crystalline silica, is characterized by chronic inflammation leading to severe pulmonary fibrotic changes that are prevalent among miners, sand blasters and quarry workers. Proinflammatory cytokines, such as TNFα and IL-1 have been implicated in the formation of these lesions. A significant association was found between disease severity and the TNFα-238 variant (OR = 4; CI, 2.4–6.8). Irrespective of disease severity, the TNFα-308 and IL-1RA + 2018 variants conferred an increased risk for the presence of disease (OR = 2.25; 95% CI, 1.4–3.6 and OR = 2.15; 95% CI, 1.3–3.5, respectively) (Yucesoy et al., 2001a, 2001b). The TNFα polymorphisms in positions -238, -376, -308 of the promoter region were also found associated with severe silicosis in South African miners ($p = 0.022, 0.016$, and 0.034, respectively) (Corbett et al., 2002).

3.2. Coal worker's pneumoconiosis (CWP)

CWP is characterized by chronic inflammation and fibrotic nodular lesions that usually leads to progressive fibrosis. In a study investigating associations between TNFα gene polymorphisms and development of CWP, the frequency of the TNFα-308 variant was significantly increased in Belgian coal miners with CWP (50%), as compared to miners without lung disease (25%) or non-miners (29%) (OR = 3.0; 95% CI; 1.0–9.0) (Zhai et al., 1998). The TNFα-308 and lymphotoxin-α (LTA) NcoI polymorphisms were investigated in a prospective epidemiological study in French coal miners differentially exposed to coal dust and cigarette smoke. While the LTA NcoI polymorphism was associated with CWP prevalence in miners with low blood catalase activity ($p = 0.05$), the TNFα-308 SNP showed an interaction with erythrocyte GSH-Px activity in individuals with high occupational exposure ($p = 0.003$) (Nadif et al., 2003). The frequency of the TNFα-308 variant was also found increased in Japanese miners with nodular CWP compared to controls (6.35% and 2.05%, $p < 0.01$) (Wang et al., 2005). Furthermore, the TNFα-308 variant was found associated with the development of a large opacity in CWP in Korean miners (28.2%) compared to those with simple CWP (13.4%) (Kim et al., 2002).

Interactions in chemokine and chemokine receptor genes with the development of CWP was investigated in French coal miners, CCR5 Δ32 and CX3CR1 V249I variants were associated with higher CT score and lower progression in CT score, respectively (Nadif et al., 2006). Associations of the CX3CR1 V249I or CCR5 Δ32 alleles with CT score and pneumoconiosis prevalence were more evident in miners with high coal

dust exposure. Their results suggested that gene–gene and gene–environment interactions influence disease susceptibility and progression.

In another study, genetic polymorphisms in *MnSOD*, *GSTM1* and *GSTT1* genes were investigated in a group of retired Chinese coal miners and no difference was found in the distribution of genotype frequencies between cases and controls (Zhai et al., 2002). They postulated that these variations may have a limited role in the ROS-induced damage in CWP development.

3.3. Progressive massive fibrosis (PMF)

PMF is a severe form of CWP, characterized by severe scarring leading to obliteration of normal lung structures. In a case-control study of ex-coal miners, no significant associations were found between individual polymorphisms in *GSTP1*, *GSTT1* and *MnSOD* genes and susceptibility to PMF. Gene–gene interactions were also analyzed but no significant association with PMF was found (Yucesoy et al., 2005). However, these findings do not exclude the possibility that, together with other genetic and environmental impairments, antioxidant genes may play a significant role in the severity of inflammatory or fibrotic lung diseases.

3.4. Chronic beryllium disease (CBD)

CBD, a rare occupational, granulomatous lung disease with similar pathological and clinical features to sarcoidosis, is caused by hypersensitivity to beryllium in a variety of industrial processes (Infante and Newman, 2004). Recent studies investigating the contribution of HLA alleles to disease processes revealed an association between HLA-DPB1 (Glu69) variation and CBD (Maier et al., 2003; McCanlies et al., 2004; Saltini et al., 2001; Sawyer et al., 2004). The TNFα-308 variant was also reported to be associated with a high level of beryllium-stimulated TNFα, and appears to be linked to disease severity (Maier et al., 2001). Recently, the TGFβ1 (codon 25) variant associated with a low TGF-β release was reported to be involved in the pathogenesis of CBD (Gaede et al., 2005).

4. Gene–gene, gene–environment interactions

As with other complex diseases, several gene–gene interactions may exist in pneumoconiosis. In silicosis, the presence of both IL-1α + 4845 and TNFα-238 variants was associated with decreased odds of moderate disease. The association between TNFα-238 and severe silicosis was greater in subjects without the IL-1α variant. A second interaction was found between IL-1RA + 2018 and TNFα-308 variants. The proportion of moderate cases increased independently with the presence of either minor variant. For severe disease, however, both IL-1RA and TNFα-308 variants were present (Yucesoy et al., 2001b). Nadif et al. showed an interaction of TNFα-308 variant with high coal dust exposure and GSH-Px activity ($p = 0.003$). They postulated that chronic oxidative stress resulting from high dust exposure may down regulate GSH-Px and high-producer TNFα genotypes modulate GSH-Px activity through the regulation of GSH levels (Nadif et al., 2003). These results suggest interactions exist between exposure and intermediate response phenotypes in the development of CWP. In the case of CBD, Be exposure and HLA-DPB1*0201-associated glutamic acid residue 69 were found to be associated with CBD. These results were confirmed and more in-depth studies suggested HLA-DP1 Glu 69 can be a diagnostic indicator of risk for development of CBD (Lombardi et al., 2001; McCanlies et al., 2004; Richeldi et al., 1993).

5. Conclusion

Genetic epidemiology offers a powerful approach to the identification of genetic variants that influence susceptibility to many multifactorial diseases. Although the pathogenesis of pulmonary fibrosis remains incompletely understood, identification and understanding the role of genetic risk factors help provide novel insights into etiology of the disease and helps to identify molecular regulators of inflammatory and fibrotic processes in the lung. In spite of some contradictory findings in SNP-disease association studies, recent advances in genotyping technology and statistically robust association study designs could lead to a better understanding of disease mechanisms and identify novel strategies for therapeutic intervention as well as provide opportunities to improve the risk assessment process.

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