Comparative Biology of the Normal Lung

Second Edition

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Role of Genetic Factors in Pulmonary Disease Susceptibility

Berran Yucesoy, Victor J. Johnson and Michael I. Luster

Chapter Outline

1. INTRODUCTION

Common human diseases are multifactorial in nature, being influenced by complex interactions between environmental, lifestyle, and genetic factors. Genetic variations and their interaction with these factors represent disease modifiers. In addition to influencing disease occurrence in the general population, they can affect disease severity or the response to specific treatment regimens. The human genome is intrinsically variable, including single nucleotide polymorphisms (SNPs), variable number tandem repeats, copy number variations, and structural changes such as deletions, duplications, and inversions. The majority of this variation is in the form of SNPs, which result from single base changes that substitute one nucleotide for another. They occur at a frequency of approximately 1 in 1000 bp throughout the genome. Approximately 50% of SNPs are located in the noncoding regions, whereas the remaining lead to either missense or synonymous (silent) mutations (Brookes, 1999; Halushka et al., 1999). SNPs that affect a phenotype are referred to as *functional* variants. Most functional SNPs do not directly affect gene expression but rather change the rate of mRNA synthesis and degradation (Collins et al., 1999; Shastry, 2009). Common SNPs with minor allele frequency greater than 1–5% in the human population generally possess low or incomplete penetrance and normally must interact with other genes or environmental factors to influence disease. Susceptibility profiles, which reflect a unique combination of multiple common risk variants, can help to define interindividual variability and more susceptible groups in the general population. Molecular epidemiological studies have identified a number of genetic variations within immune/inflammatory genes as susceptibility factors for common immune-mediated/chronic inflammatory diseases, including many pulmonary disorders. Data are now accumulating on their role in diseases of occupational and environmental origin. Some susceptibility factors are shared between different pulmonary disorders, indicating a common immunological and genetic background. This chapter focuses on immunogenetic predisposition to pulmonary disorders, particularly those that can be related to occupational exposures such as occupational asthma (OA), chronic beryllium disease (CBD), coal workers' pneumoconiosis (CWP), and silicosis.

2. SNP DISEASE ASSOCIATIONS

Genetic association studies identify genes that include inherited variants that influence disease risk and, in certain instances, responses to therapeutic treatments or environmental exposures. Linkage disequilibrium, which is a nonrandom association of genes between loci, gene–gene, and gene–environment interactions and the existence of multiple disease loci, are the major factors to be considered for the interpretation of results. The candidate gene

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approach has been commonly used in searching for susceptibility variants. These studies use biological information with regard to disease pathogenesis and select candidate genes on the basis of prior information from animal models, in vitro/in vivo experiments, or data-mining for disease-associated genes (Hoh and Ott, 2004). On the other hand, genome-wide association studies (GWAS) provide an opportunity for studying dense sets of SNPs across the genome simultaneously for associations. Because there is no a priori hypothesis, this approach has the potential to identify and test new candidate SNPs and regions. Although GWAS platforms do not cover the entire genome and large sample sizes are needed to compensate for the multiple comparisons, using this approach, a number of candidate regions/genes for complex phenotypes have been identified (Michel et al., 2010). For example, chromosomal regions 4q, 5q31, 6p21, 9q21, 10p, 12q, 13q, 16p12, and 17q21 were found to be associated with asthma/allergy and related phenotypes (Blumenthal, 2005; Akhabir and Sandford, 2011; Hancock et al., 2009; Potaczek and Kabesch, 2011; Hirota et al., 2011), and genetic markers on chromosomes 4, 8, 12, and 19 were found to contribute to susceptibility to chronic obstructive pulmonary disease (COPD) (DeMeo et al., 2004; Hersh et al., 2006; Cho et al., 2011a; Pillai et al., 2009).

3. GENE–ENVIRONMENT INTERACTIONS

Complex diseases result from interactions between multiple genes, lifestyle, and environmental/occupational factors. Gene–environment studies investigate the interaction between common susceptibility variants and commonly encountered exposures. Exposure characteristics (e.g., dose, duration) may overwhelm differences associated with genetic variability; therefore, they are of primary consideration in genetic association studies. Occupational diseases may differ from other environmentally induced diseases because there is a quantifiable environmental component behind gene–environment interactions.

Environmental/occupational molecular epidemiology studies have primarily focused on examining hypothesis-driven associations between exposures and specific genetic variations. In this respect, a number of susceptibility markers have been identified in several occupational lung diseases, such as silicosis, asthma, CBD, and CWP (Yucesoy et al., 2001a; McCanlies et al., 2004; Ates et al., 2008; Bernstein et al., 2006). These studies have provided strong evidence that the pathogenesis of occupational lung diseases involves gene–environment interactions. The common link among these diseases are chronic inflammation and alterations in host immunity, which suggests that exposed individuals who have susceptibility variants that influence immune and inflammatory responses are more likely to develop disease than those without the susceptibility variants. The remainder of this chapter discusses lung diseases prompted by occupational exposures and gene–environment interactions using several examples. A simplified, theoretical model of how genetic and environmental, occupational, and lifestyle factors may interact to induce pulmonary disease is shown in Figure 1.

4. GENETIC SUSCEPTIBILITY AND GENE–ENVIRONMENT INTERACTIONS IN PULMONARY DISEASES

4.1 Occupational Asthma

Asthma is an inflammatory airway disease characterized by airway hyperreactivity, chronic eosinophilic inflammation, and mucus hypersecretion and is one of the most significant examples of gene–environment interaction causing disease. In addition to exposures to an allergen (e.g., diisocyanates), a number of triggers such as environmental pollutants (e.g., O_3, tobacco smoke, diesel exhaust), domestic exposures (e.g., bioaerosols containing endotoxin), and/or viral respiratory infections interact with host susceptibility factors (Kleeberger and Peden, 2005). Linkage studies have suggested a number of candidate genes that are related to asthma phenotypes. In particular, variants of interleukin (IL)-4, IL-4RA, IL-13, β-2 adrenergic receptor (ADRB2), human leukocyte antigen (HLA)-DR, the β-subunit of the high-affinity IgE receptor (FceRI), and CD14 genes have been consistently associated with asthma-related phenotypes in independent association studies (Ober and Hoffjan, 2006; Postma and Koppelman, 2009; Vercelli, 2008; Ober and Yao, 2011). The genetic variants identified to date had only small effects and unknown inheritance patterns indicating complex polygenic nature of disease.

Among occupational exposures, the diisocyanates are the most frequently reported cause of OA in the workplace. These agents are widely used in polymerization reactions for manufacturing surface coatings, varnishes, paints, urethane foams, insulation, and adhesives. Genetic studies investigating the immunopathogenesis of OA have focused largely on the HLA alleles. HLA class II molecules are involved in the presentation of intracellularly processed peptides to CD4+ T-helper cells. These molecules are highly polymorphic and the variations in their protein structure help to determine the specific epitopes presented to T cells. A number of significant associations have been found between OA and HLA class II molecules. The HLA DQB1*0503 and the allelic combination DQB1*0201/0301 are associated with susceptibility to diisocyanate asthma (DA), whereas the DQB1*0501 allele and the DQA1*0101-DQB1*0501-DR1 haplotype are believed to be protective (Bignon et al., 1994). Others

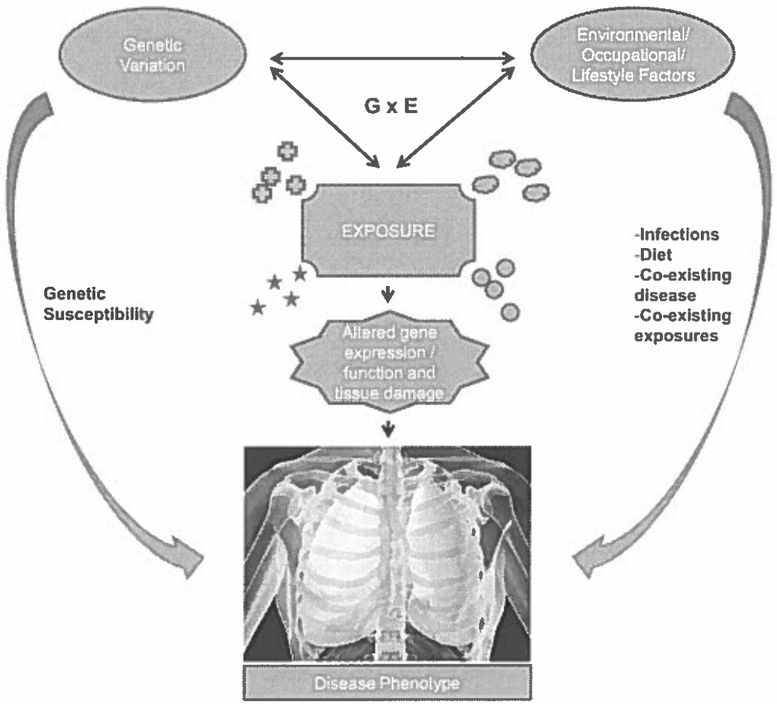

FIGURE 1 Interaction between genetic and environmental/occupational/lifestyle factors in the development of pulmonary disease.

reported increased frequency of the DQA1*0104 and DQA1*0101-HLA-DQB1*0501 in DA and asymptomatic exposed workers, respectively (Mapp et al., 2000). In another study, a significantly higher proportion of subjects with DA were found to express the HLA-DQB1*0503-associated aspartic acid at residue 57 (Balboni et al., 1996). On the other hand, the HLA haplotypes DRB1*15-DPB1*05, and HLA DRB1*1501-DQB1*0602-DPB1*0501 were reported as a susceptibility marker for the development of toluene diisocyanate-asthma in Koreans (Kim et al., 2006; Hur et al., 2009). In addition, an association was found between DRB1*0901-DQB1*0303-DPB1*0501 haplotype and the presence of serum-specific IgG in methylene diisocyanate-exposed workers (Hur et al., 2009).

Similarly, HLA class 2 alleles were found to be associated with OA caused by other low-molecular-weight agents. Workers with red cedar asthma had a higher frequency of HLA DQB1*0603 and DQB1*0302 alleles compared to exposed control subjects and a reduced frequency of DQB1*0501 allele (Horne et al., 2000). They also reported an increased frequency of the DRB1*0401-DQB1*0302 haplotype and a decreased frequency of the DRB1*0101-DQB1*0501 haplotype. In another study, the DQB1*0501 allele was found to be more prevalent in workers exposed to organic acid anhydrides than in controls (Jones et al., 2004). The protective effect of DQB1*0501 for other low-molecular-weight sensitizers (isocyanates and plicatic acid) suggests differential affinities of these chemicals for specific class II molecules. In addition, a significant excess of HLA-DR3 was reported in subjects with specific IgE antibody to trimellitic anhydride (Young et al., 1995) and positive skin prick tests to ammonium hexachloroplatinate (Newman Taylor et al., 1999).

Several studies reported associations between HLA alleles and OA caused by high-molecular-weight allergens. While a higher prevalence of HLA-B15 and DR4 was reported in workers with laboratory animal allergy (Low et al., 1988), the prevalence rate of HLA-B16 was higher in symptom-free subjects (Sjostedt et al., 1996). In another study, the HLA-DR7 was found to be associated with work-related respiratory symptoms and specific IgE to rat urinary proteins. HLA-DR3 was reported to be protective against sensitization (Jeal et al., 2003). Pacheco et al., reported a significant gene–environment interaction

affecting airway function in laboratory animal workers (Pacheco et al., 2010). More highly endotoxin-exposed workers with CD14 -1619G allele have significantly lower forced expiratory volume in 1 s (FEV_1) and forced expiratory flow (FEF 25–75) percent predicted than those with CD14/-1619AA alleles. The gene–environment effect was marked in atopic workers.

Based on their role in allergen-induced airway inflammation, Bernstein et al. investigated SNPs in immune response genes (IL-4Rα, IL-13, and CD14) in a group of workers with DA as determined by specific inhalation challenge—the criterion standard for establishing allergic asthma. The results demonstrated increased frequencies of IL-4RA I50V allele and combinatorial genotypes of IL4RA (I50V), IL-13 (R110Q), and CD14 (C159T) in workers with DA, supporting the notion that immune mechanisms play an important role in the pathogenesis of DA (Bernstein et al., 2006, 2011). Many of the examples of OA gene–environment interactions have been collected and tabulated in Table 1.

4.2 Chronic Beryllium Disease

CBD is a granulomatous lung disease caused by beryllium (Be) exposure in the workplace. CBD continues to occur in industries where Be is manufactured and processed, such as aerospace, nuclear, automotive, and electronics. Be exposure leads to a cell-mediated hypersensitivity (delayed, type IV) reaction, in which Be forms haptens with native proteins, leading to the production of the specific allergen (Maier et al., 2003). Accumulation of Be-specific CD4 (+) T cells and persistent lung inflammation play a key role in the immunopathogenesis of CBD. A number of molecular epidemiology studies showed that the presence of glutamic acid in position 69 of the B1 chain of the HLA-DPB1 molecule (coded for by *HLA-DPB1E69* also known as HLA-DPB1Glu69 or simply Glu69) confers an increased risk for both BeS and CBD (McCanlies et al., 2004; Maier et al., 2003; Richeldi et al., 1993; Wang et al., 2001; Fontenot et al., 2000; Lombardi et al., 2001). Thus, the allele frequency for *HLA-DPB1E69* is highest in workers with CBD (F = 0.38–74), next highest in BeS (F = 0.20–0.60), and least in nondiseased/nonsensitized workers (F = 0.18–0.35) (McCanlies et al., 2004; Maier et al., 2003; Wang et al., 2001; Rossman et al., 2002; Saltini et al., 2001; Wang et al., 1999). Importantly, a dose-dependent effect of *HLA-DPB1E69* alleles has been demonstrated, suggesting that Glu69 is a potential marker of disease severity in addition to overall disease risk (Maier et al., 2003). Although *HLA-DPB169* is more frequent in individuals with BeS and CBD, 30–40% of exposed workers carrying *HLA-DPB1E69* do not develop CBD or BeS (McCanlies et al., 2004; Maier et al., 2003; Samuel and Maier, 2008). This suggests that other host and environmental factors likely play key roles in the etiology of CBD. Studies investigating the interaction between the *HLA-DPB1E69* and Be exposure have shown independent and additive effects of Glu69 carriage and Be exposure in the development of BeS and CBD (Richeldi et al., 1997; Van Dyke et al., 2011). The *HLA-DQB1G86* and *HLA-DRB1S11* alleles were reported to be more frequent in individuals with CBD (Rossman et al., 2002). Maier et al., found a reduced frequency of the *HLA-DRB1*01* and *DQB1*05* alleles in workers with CBD. They also reported that *DRB1*13* and *DQB1*06* were associated with CBD in the absence of Glu69 (Maier et al., 2003). One study showed that the *DRBE71* allele is a risk factor for both CBD and BeS in the absence of Glu69 and highlighted the importance of interactions between peptides and T cells in the development of CBD (Rosenman et al., 2010). Chemically specific Be–protein interactions were also investigated using a computational approach. Glu69 alleloforms with the greatest negative surface charge were found to confer the highest risk for CBD and, irrespective of allele, equal risk for BeS (Snyder et al., 2008). Current HLA research includes investigating whether risk is associated with any or only certain Glu69 alleles or allelic combinations. In a recent study, *HLA-DPB1* and *HLA-DRB1* loci were typed at the allele level in subjects with BeS, CBD, and nonaffected, BE-exposed controls. The *DRBE71* was reported to be a risk factor for CBD and BeS in the absence of *DPBE69* (Rosenman et al., 2011).

Non-HLA genetic studies have also identified some significant associations. Maier et al. investigated eight SNPs within the *CCR5* gene which is implicated in the chemotaxis and activation of leukocyte subsets. The results showed that *CCR5-5663* and *-3458* variants were associated with worsening pulmonary function over time in CBD (Sato et al., 2010). The *-509C* and codon *10T* variants of the transforming growth factor–beta1 (*TGFβ*) gene, a cytokine which helps control the fibrotic/Th1 response, were found to be associated with more severe granulomatous disease in CBD (Jonth et al., 2007). While Saltini et al. reported an association between the *TNFα-308*02* variant and BeS and CBD, this result was not confirmed in a large population-based study (Saltini et al., 2001; McCanlies et al., 2007). On the other hand, Dotti et al., reported that the *TNFα -308A* and *-857T* variants are significantly associated with BeS (Dotti et al., 2004). McCanlies et al., showed that *IL-1α-1142, -3769*, and *-4697* variants were significantly associated with CBD compared to individuals with BeS or nonsensitized workers after adjusting for Glu69 status (McCanlies et al., 2010). These results suggested that the formation of granulomas in CBD may require an independent inflammatory response controlled by genes unrelated to Be recognition.

TABLE 1 Genetic Variants of Inflammatory/Immune Response Genes Involved in Occupational Asthma

Disease	Gene/Variant	Effect Size (OR, RR, or *P*)	Reference	Population Case/Control
Occupational Asthma				
Diisocyanates (TDI)	HLADQB1*503	RR 9.8	Bignon et al. (1994)	56/32
	HLA-DQB1*0201/0301	RR 9.5	Bignon et al. (1994)	
	HLA-DQB1*501	RR 0.1	Bignon et al. (1994)	
	HLA-DQA1*0101-*0102	RR 0.1	Bignon et al. (1994)	
Diisocyanates (TDI)	HLA-DQB1*503	RR 2.9	Balboni et al. (1996)	30/12/126[a]
	HLA-DQB1*501	RR 0.04	Balboni et al. (1996)	
Diisocyanates (TDI)	HLA-DQB1*0503	P = 0.009	Mapp et al. (2000)	67/27
	HLA-DQB1*0501	P = 0.01	Mapp et al. (2000)	
	HLA-DQA1*0101	P = 0.004	Mapp et al. (2000)	
	HLA-DQA1*0104	P = 0.005	Mapp et al. (2000)	
Diisocyanates (TDI)	HLA-DRB1/*1501- DQB1/*0602-DPB1/*0501	OR 4.4 (1.5–13.1)	Choi et al. (2009)	84/47/127[a]
Diisocyanates (HDI)	IL-4RA(I50V) II + IL-13(R110Q) RR + CD14 (C159T) CT	OR 3.86 (1.26–12.0)	Bernstein et al. (2011)	103/115/150[a]
Acid anhydrides	HLA-DR3	OR 6.0	Young et al. (1995)	30/30
	HLA-DQ5	OR 4.3 (1.7–11.0)	Jones et al. (2004)	52/73
	HLA-DQB1/*0501	OR 3.0 (1.2–7.4)	Jones et al. (2004)	
	HLA-DQ-DR1	OR 3.0 (1.2–11.0)	Jones et al. (2004)	
Laboratory animal	HLA-DR1/*07	OR 1.8 (1.1–2.9)	Jeal et al. (2003)	109/397
	HLA-DR1/*03	OR 0.5 (0.3–1.0)	Jeal et al. (2003)	
Laboratory animal	TLR4/8551G	OR 2.5 (1.5–5.5)	Pacheco et al. (2008)	335
Platinum salts	HLA-DR3	OR 2.3 (1.0–5.6)	Newman Taylor et al. (1999)	44/57
	HLA-DR6	OR 0.4 (0.2–0.8)	Newman Taylor et al. (1999)	
Red cedar	HLA-DQB1/*0302	OR 4.9 (1.3–18.6)	Horne et al. (2000)	56/63
	HLA-DQB1/*0603	OR 2.9 (1.0–8.2)	Horne et al. (2000)	
	HLA-DQB1/*0501	OR 0.3 (0.1–0.8)	Horne et al. (2000)	
	HLA-DRB1/*0401-DQB1*0302	OR 10.3	Horne et al. (2000)	
	HLA-DRB1/*0101-DQB1*0501	OR 0.3	Horne et al. (2000)	
Trimellitic anhydride	HLA-DR3	OR 16.0	Young et al. (1995)	30/30
Wheat flour	TLR4/-2027 GG	OR 0.16 (0.04–0.73)	Cho et al. (2011b)	381

[a]*Case/asymptomatic exposed/unexposed normal control.*

4.3 Silicosis

Silicosis is an interstitial lung disease resulting from inhalation of crystalline silica or quartz. The disease is characterized by chronic inflammation leading to severe pulmonary fibrotic changes and is prevalent in miners exposed chronically to dusts and other irritants. In a study conducted in underground coal miners participating in the National Coal Workers Autopsy Study (NCWAS), a strong association was found between severity and presence of silicosis and variants of TNFα (−308) and IL-1RA (+2018) genes (Yucesoy et al., 2001a). These results supported previous experimental and clinical data demonstrating the importance of TNFα and IL-1 in regulating the development of silicotic lesions. Another study was conducted in the NCWAS population to investigate associations between genetic variability within genes involved in inflammatory and fibrotic processes and susceptibility to progressive massive fibrosis (PMF). Although, there was no significant single−locus association, the polygenotype of VEGF +405/ICAM-1 +241/IL-6 -174 (C-A-G) conferred an increased risk for PMF (Yucesoy et al., 2008). These results suggested that particular SNPs in the VEGF, ICAM-1, and IL-6 genes may influence the interaction and amplification process between these genes, and play an important role in the pathogenesis of pulmonary fibrosis. In studies of South African miners, TNFα polymorphisms at positions -238, -376, -308 of the promoter region were found to be associated with severe silicosis (Corbett et al., 2002). IL-12p40 SNPs were also studied in silicosis for their potential influence on inflammatory response by affecting Th1/Th2 cytokine balance. Stanilova et al. found an association between IL-12BA/C 3′UTR SNP and silicosis severity in Bulgarian miners (Stanilova et al., 2007). The minor allele carriers of the IL-12Bpro promoter polymorphism were associated with a protection against susceptibility to silicosis. This was attributed to the higher production of IL-12p40 in homozygous wild-type patients (Stanilova et al., 2008). As demonstrated for other occupational lung diseases, HLA alleles were also found to be related to silicosis pathogenesis. Honda et al., reported an association between increased frequency of the HLA-Bw54 allele and silicosis (Honda et al., 1993). HLA-DR gene locus (HLA-DRB1 and DQB1 alleles) was also found to be related to silicosis susceptibility in Asian miners (Ueki et al., 2001; Yuan et al., 2002).

4.4 Coal Workers' Pneumoconiosis

CWP is characterized by chronic inflammation that usually leads to fibrosis due to irritation caused by dust exposure. Although, the mechanisms of susceptibility to disease development and progression are not clear, several studies have proposed a genetic component (Borm and Schins, 2001). In a study investigating associations between TNFα gene polymorphisms and development of CWP, the frequency of the TNFα -308 variant was significantly increased in miners with CWP (50%), as compared with miners without lung disease (25%) or non-miners (29%) (Zhai et al., 1998). Similarly, the frequency of TNFα -308 variant was greater in Korean CWP patients (20.6%) and in patients with a large opacity (28.2%) in comparison with patients with simple CWP (13.4%) (Kim et al., 2002). The presence of the minor allele was significantly associated with increased relative risk of complicated CWP. In another study, the -308 A allele frequency was found to be higher in patients with CWP and nodular CWP compared to controls and subjects with PMF (Wang et al., 2005). The TNFα -308 and lymphotoxin-α (LTA) NcoI polymorphisms were also investigated in a prospective epidemiological study in miners differentially exposed to coal dust and cigarette smoke. While the LTA NcoI polymorphism found associated with CWP prevalence in miners with low blood catalase activity, the TNFα -308 SNP showed an interaction with erythrocyte GSH-Px activity in individuals with high occupational exposure (Nadif et al., 2003). The TNFα -238 and -308 polymorphisms were associated with CWP development and severity in Turkish coal miners, respectively (Ates et al., 2008). They also reported a protective effect of the IL-6 -174 variant in the development and severity of CWP. Genetic variants in IL-18, chemokines and chemokine receptors have also been studied in relation to CWP. The IL18 -137C allele was found to be associated with lower and slower progression of the computed tomography (CT) score and lower pneumoconiosis prevalence in a group of miners (Nadif et al., 2006a). The same group also reported an association between the CX3CR1 V249I and lower CWP prevalence, especially in miners with high dust exposure. In addition, the CX3CR1 I249 allele was significantly associated with lower and slower progression of the CT score in CCR5 Delta32 carriers (Nadif et al., 2006b). Recently, the IL-4 -590 CT/CC genotypes were reported to be associated with a significantly decreased risk of CWP in a Chinese population, particularly among subgroups of age <65 years and dust exposure years ≥26 years (Wang et al., 2011).

4.5 Lung Function Decline

Endotoxin exposure confers an increased risk for nonatopic asthma and lung function decline in exposed workers. In a study investigating associations between TNFα -308 and LTA (252A/G rs909253) polymorphisms, endotoxin exposure and lung function in cotton workers, endotoxin exposure was associated with faster FEV1 decline among subjects carrying high producer TNFα -308 A allele. The annual changes in FEV1 were higher in G allele carriers of the LTA polymorphism. The effect modification of these variants was prominent in never smokers when joint effects of endotoxin exposure and smoking were considered (Zhang et al., 2007). Another study conducted in male grain handlers demonstrated that years in the grain industry is an effect modifier between TNFα -308 genotype and longitudinal decline in FEV1. The annual FEV1 decline for grain workers carrying the TNFα -308 G allele and worked in the grain industry for <10 years were lower by comparison to those of grain workers with AA genotype and had been in the industry for <10 years (Pahwa et al., 2009).

TABLE 2 Genetic Variants of Inflammatory/Immune Response Genes Involved in Metal, Mineral, and Organic Dust-Related Pulmonary Diseases

Disease	Gene/Variant	Population Case/Control	Effect Size (OR or P)	Reference
CBD				
	HLA-DPB1/E69	104/64/727[a]	9.4 (5.4−16.6)	McCanlies et al. (2004)
	HLA-DQB1/G86	22/23/82	P < 0.04	Rossman et al. (2002)
	HLA-DRB1/S11		P < 0.03	Rossman et al. (2002)
	CCR5/-3458	88/86/173[a]	P < 0.0001	Sato et al. (2010)
	TGFβ1/-509	130/135	P = 0.01	Jonth et al. (2007)
	IL-1A/-1142	85/61/730[a]	3.02 (1.36−6.70)	McCanlies et al. (2010)
	IL-1A/-3769		2.51 (1.21−5.19)	McCanlies et al. (2010)
	IL-1A/-4697		2.56 (1.24−5.29)	McCanlies et al. (2010)
Silicosis				
	TNFα/-308	325/164	2.25 (1.4−3.6)	Yucesoy et al. (2001a)
	TNFα/-238		4.00 (2.4−6.8)	Yucesoy et al. (2001a)
	IL-1Ra/+2018	318/163	2.15 (1.4−3.3)	Yucesoy et al. (2001b)
	TNFα/-308, -238	121/120	P = 0.022, 0.034	Corbett et al. (2002)
	IL-12/A/C-3′UTR	62/138	6.56 (1.7−25.6)	Stanilova et al. (2007)
	HLA/Bw54	43/315	P < 0.05	Honda et al. (1993)
CWP				
	TNFα/-308	78/56	3.0 (1.0−9.0)	Zhai et al. (1998)
	TNFα/-308	80/54	3.18 (1.25−8.10)	Kim et al. (2002)
	TNFα/-308	84/44/122[b]	P < 0.01	Wang et al. (2005)
	TNFα/-238	67/92	3.79 (1.37−10.46)	Ates et al. (2008)
	TNFα/-308		2.84 (1.08−7.39)	Ates et al. (2008)
	IL-6/-174		0.48 (0.21−0.93)	Ates et al. (2008)
	IL-18/-137C	66/134	P = 0.02	Nadif et al. (2006a)
	CCR5/Δ32 CX3CR1/V249I		P = 0.03	Nadif et al. (2006b)
	IL-4/-590	556/541	0.74 (0.58-0.05)	Wang et al. (2011)
Organic Dust Exposure/Lung Function				
Endotoxin	TNFα/-308	263/230		Zhang et al. (2007)
Grain dust	TNFα/-308	243	P < 0.05	Pahwa et al. (2009)
Endotoxin	CD14/-260	408	P ≤ 0.01	Smit et al. (2011)

[a]*CBD/Be-sensitized/control.*
[b]*CWP/PMF/control.*

The association between occupational endotoxin exposure and wheeze in agricultural workers was found to be significantly modified by genetic variants in the CD14 (-260 C/T, rs2569190) and MD2 (lymphocyte antigen 96, rs10808798 T/C) genes. The prevalence of wheeze was increased with increasing endotoxin concentration in individuals with the CD14 and MD2 major alleles. The carriers of the functional CD14 -260C allele were more responsive to endotoxin exposure than T allele homozygotes (Smit et al., 2011). Some of the associations related to metal, mineral, and organic dust-induced pulmonary diseases are summarized in Table 2.

CONCLUSIONS

Molecular epidemiology offers a powerful approach to the identification of genetic variants that influence susceptibility to many common diseases. The guidance from human genetic studies may lead to better animal models and in vitro systems to investigate critical pathways and molecular regulators of disease processes. Despite the rapid growth of publications, some of the genetic associations lack consistency across different studies. The inconsistency can be explained by a number of factors including the differences in study populations, phenotype characterization, exposure assessment, characterization of other environmental exposure (e.g., air pollution, smoking), intermediate phenotypes (e.g., airway hyperresponsiveness), statistical inconsistencies, and other potentially modifiable risk factors such as lifestyle. In spite of sometimes contradictory findings in association studies, a growing number of susceptibility markers have been identified for complex diseases using large, well-characterized DNA collections, and high throughput genotyping technologies. Understanding how the genetic variability between individuals at the sequence level translates into variation in disease susceptibility and the interaction between genetic and environmental/occupational factors will provide new insights into disease pathogenesis as well as opportunities into developing novel therapeutic, preventive, and educational strategies.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Appendix 1

Architecture of Nasal Passages and Larynx

TABLE 1 Summary of Available Morphometry Data on Nasal Passages, Paranasal Sinuses, and Larynx

	Nasal Cavity						Paranasal Sinuses			Larynx		
	Length	Maximum Vertical Height	Perimeter	Cross-Sectional Surface Area	Surface Area of Wall	Volume	Wall Width and Height	Surface Area of Wall	Volume	Linear Measurements	Diameter	Surface Area
Human[a]	+	+		+	+	+	+	+	+	+		
Rhesus monkey	+	+	+	+	+	+	+	+	+			
Beagle dog	+	+	+	+	+	+						
Rat: Sprague-Dawley	+	+	+	+	+	+						
F 344	+		+	+	+	+						
B6C3F1 mouse	+				+	+						
Guinea pig	+		+	+	+	+						
Other species					+[b]	+[c]				+[d]	+[e]	

[a] *Many additional measurements.*
[b] *Antelope, vole, dik dik, camel, elephant seal.*
[c] *Camel, antelope.*
[d] *Large cats, rabbit, sheep.*
[e] *Rabbit.*