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Genetic risk factors for chronic obstructive pulmonary disease

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Summary

Cigarette smoking is the major risk factor for chronic obstructive pulmonary disease (COPD). However, only a minority of cigarette smokers develop symptomatic disease. Family and twin studies suggest that genetic factors also contribute to the development of COPD. We present a detailed literature review of the genes which have been investigated as potential risk factors for this disease.

Key words: chronic obstructive pulmonary disease; polymorphisms; genetics

Introduction

There is no doubt that the main risk factor for chronic obstructive pulmonary disease (COPD) is cigarette smoking. However, it is estimated that only 10–20% of chronic heavy smokers will develop symptomatic COPD [1]. There is clearly a relationship between smoking history and decline in lung function [2]. However, smoking habits (i.e. pack years and duration of smoking) have been estimated to account for only ~15% of the variation in FEV_1 levels [2]. Hence other factors must contribute to the development of COPD. Environmental risk factors such as childhood viral respiratory infections, latent adenoviral infections and air pollution have been identified. In this review we discuss the different candidate genes likely to be involved in the pathogenesis of this disease.

Genetic epidemiology of COPD

COPD is known to aggregate in families [3–5]. Although familial aggregation could be due to environmental factors, there is considerable evidence in favour of a genetic basis for COPD. Several investigators have shown increased prevalence of COPD in the relatives of cases, compared with the prevalence of COPD in relatives of controls [4, 6–12]. The increased prevalence could not be explained by differences in other known risk factors. In addition, there is a higher correlation of lung function between parents and children or between siblings than between spouses [7, 13–15]. Finally, the prevalence of COPD and similarity in lung function decrease with increased genetic distance [4, 16]. However, none of these approaches provides definitive evidence for the existence of genetic risk factors for COPD.

Twin studies provide a more robust means of estimating the genetic contribution to variability (i.e. heritability) in lung function. Comparisons of monozygotic (MZ) and dizygotic (DZ) twins can be used to assess the relative importance of genetic and environmental effects, since MZ twins share 100% of genes while DZ twins share only 50%. In these studies, the correlation of pulmonary function in MZ twins is compared with that in DZ twins [16–23], and heritability, which is the proportion of phenotypic variance due to genes, can be used to quantify the degree of genetic contribution. Estimates of heritability for FEV_1 range from 0.5–0.8.

The pattern of inheritance of pulmonary function can also be followed in families and inferences can be drawn concerning its genetic component. This approach is known as segregation analysis and the results of such studies have confirmed a significant genetic component in pulmonary function [24–27]. The results of most of these studies have indicated that the genetic component is composed of several genes, each with a small effect, rather than a single major gene.

The genes that contribute to the development of COPD may do so via several different mechanisms. The twin studies and segregation analyses

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cited above used lung function as their phenotype and often studied non-smokers. The familial factors identified by these studies may therefore contribute to the level of lung function irrespective of susceptibility to the detrimental effects of cigarette smoke. A phenotype that may be more clinically relevant is the rate of decline in lung function in response to cigarette smoke. For example, Silverman et al. [28] showed no significant decrease in lung function in the non-smoking relatives of early-onset COPD patients. This suggests that the genetic risk factors present in these families only predispose to COPD in individuals who smoke. Another phenotype that may be relevant to COPD is the age at which lung function begins to decline. The decline in lung function may start earlier in COPD even if the rate of decline is normal. It is also possible that some genes lead to the development of airflow obstruction by loss of elastic recoil resulting in emphysema, whereas others contribute to chronic airway inflammation resulting in airway narrowing.

Candidate genes for COPD

COPD is characterised by a slowly progressive irreversible airflow obstruction which is due to peripheral airway inflammation and loss of lung elastic recoil resulting from parenchymal destruction. Many inflammatory cells, mediators and enzymes are involved, but their relative importance is still poorly understood. There is likely to be a complex interplay between genetic and environmental factors and many different genes will be involved. The genes which have been implicated in the pathogenesis of COPD are involved in antiproteolysis, metabolism of toxic substances in cigarette smoke, airway hyperresponsiveness and the inflammatory response to cigarette smoke. The genes involved or potentially involved in the pathogenesis of COPD are summarised in figure 1.

Proteases – antiproteases

Severe alpha-1-antitrypsin deficiency

Alpha-1-antitrypsin (AAT) is an acute phase protein synthesised predominantly in the liver, but also by alveolar macrophages, and provides the major defence against neutrophil elastase. In 1963, Laurell and Eriksson demonstrated that individuals who had extremely low levels of AAT had an increased prevalence of emphysema [29]. Subsequently, it was shown that AAT deficiency followed a simple Mendelian pattern of inheritance and was usually associated with the Z isoform of AAT [30–32]. The two common deficiency variants of AAT, S and Z, result from point mutations in the AAT gene [33–35] and are named on the basis of their slower electrophoretic mobility on isoelectric focusing analysis compared with the normal M allele [36]. Homozygosity of the Z variant (Glu342Lys) results in a severe deficiency characterised by plasma AAT levels of ~10% of the normal M allele. Individuals with the ZZ phenotype have a clearly accelerated rate of decline in lung function [37, 38], sometimes even in the absence of smoking [39, 40]. However, the homozygous state is rare in the population [41, 42] and thus can explain only a small percentage of genetic susceptibility to cigarette smoke.

Despite the strong association of the ZZ geno-

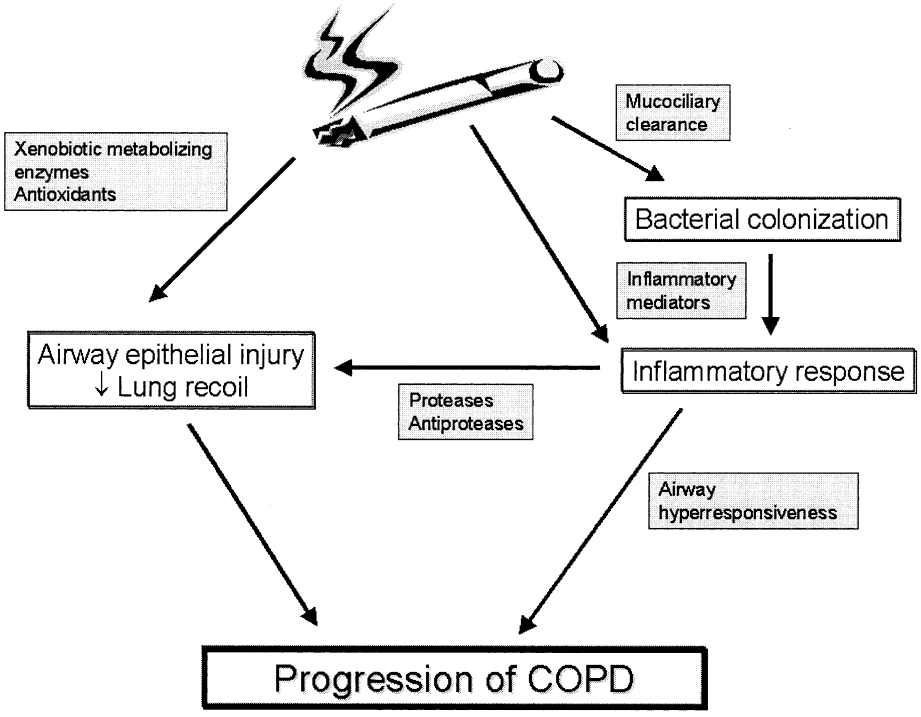

Figure 1

Summary of pathways and possible candidate genes involved in the pathogenesis of COPD.

Table 1

Summary of candidate genes and polymorphisms implicated in the pathogenesis of COPD. AAT: α_1-antitrypsin, AACT: α_1-antichymotrypsin, A2M: α_2-macroglobulin, MMP: matrix metalloproteinase, EPHX1: microsomal epoxide hydrolase, GST: glutathione S-transferase, HMOX1: heme oxygenase-1, CYP1A1: Cytochrome P4501A1, VDBP: vitamin D binding protein, TNF: tumour necrosis factor-α, IL1: interleukin-1, IL1RN: interleukin-1 receptor antagonist, CFTR: cystic fibrosis transmembrane conductance regulator, ADRB2: β_2-adrenergic receptor

Candidate gene	candidate risk allele	effect of risk allele	prevalence of risk allele	association studies
AAT	Z (Lys^{342})	α_1-AT deficiency (15% of normal)	0.006–0.024 in Caucasians, rare in other populations	ZZ individuals have a marked increased in risk for COPD. MZ individuals have a modest increase in risk
	S (Val^{264})	α_1-AT deficiency (60% of normal)	0.003–0.115 in Caucasians, rare in other populations	generally believed not to increase risk for COPD
	3' (1237A)	Attenuated up-regulation of gene expression *in vitro*	0.053–0.112 in Caucasians, 0.241 in blacks	conflicting data regarding risk for developing COPD
AACT	Ala^{227}	α_1-ACT deficiency (51% of normal)	0.004–0.020 in Caucasians	associated with COPD in some populations
	Thr^{-15}	none known	0.504 in Japanese	associated with COPD despite lack of α_1-antichymotrypsin deficiency
A2M	Tyr^{972}	predicted to interfere with protein function	0.017 in Caucasians	identified in one COPD patient. No convincing epidemiological data concerning this polymorphism
MMP1	-1607GG	creates a binding site for the ETS-1 transcription factor and was associated with higher levels of *in vitro* gene expression	0.528 in Caucasians, 0.623 in Japanese	paradoxically associated with lower rate of decline of lung function
MMP12	Asn^{357}	none known	0.049 in Caucasians	*MMP1*-1607G in combination with *MMP12* Asn357 was associated with rapid decline of lung function
EPHX	His^{113}	in combination with His^{139} results in decreased activity (59% of normal)	0.285–0.308 in Caucasians, 0.436–0.513 in Japanese. 0.579 in Koreans	associated with COPD and rate of decline of lung function in Japanese and white populations
	His^{139}	in combination with His^{113} results in decreased activity (59% of normal)	0.798–0.855 in Caucasians, 0.807–0.856 in Japanese, 0.862 in Koreans	in combination with His^{113} associated with COPD and rate of decline of lung function
GSTM1	Null	complete loss of protein production	Homozygosity for null allele: 64.5% in Koreans, 47.1–53.4% in Caucasians	increased risk of COPD shown in white populations
GSTP1	Ile^{105}	reduced catalytic activity for some xenobiotic substrates	0.820 in Japanese, 0.645 in Caucasians	associated with COPD in the Japanese population
HMOX1	(GT)n promoter repeat	modulation of gene transcription rate in vitro	At least 22 alleles in Caucasians and 20 alleles in Japanese	large repeat size associated with emphysema and decreased promoter activity
CYP1A1	Val^{462}	increase in catalytic activity (2-fold above normal)	0.032–0.069 in Caucasians	associated with COPD but only in patients who also had lung cancer
VDBP	1F	possible influence on rate of conversion to a pmacrophage activating factor	0.144–0.155 in Caucasians, 0.685 in blacks, 0.482 in Japanese	associated with increased risk of COPD in Caucasians and Japanese
	2	possible influence on rate of conversion to a macrophage activating factor	0.087–0.321 in Caucasians, 0.143 in blacks, 0.220 in Hispanics, 0.231 in Chinese, 0.244 in Japanese	associated with decreased risk of COPD in Caucasians
TNF	–308A	increased TNF in vitro and in vivo in some studies	0.172–0.183 in Caucasians, 0.008–0.078 in Japanese	associated with COPD in one Japanese study but to date this has not been replicated in Japanese or white subjects
IL1	–511T	increased levels of IL1 and IL1RN	0.330 in Caucasians, 0.508 in Japanese	in combination with IL1RN allele 2 associated with attenuated rate of decline of lung function
IL1RN	2	increased levels of IL1 and IL1RN	0.272 in Caucasians	in combination with IL1 -511T associated with attenuated rate of decline of lung function
CFTR	IVS8-5T	reduced CFTR expression	0.078 in Caucasians	conflicting data regarding the role of this polymorphism in COPD
	Met^{470}	none known	0.325–0.447 in Caucasians	association with COPD in one study
ADRB2	Gln^{27}	decreased resistance to receptor down-regulation	0.526–0.652 in Caucasians, 0.683 in Turks, 0.928 in Chinese	association between heterozygosity of this polymorphism and rapid decline of lung function

type with early-onset COPD, the clinical course of the disease is highly variable [43]. Although cigarette smoking plays an important role in determining this variability [44], the rate of decline of lung function in ZZ subjects who are lifelong non-smokers is also highly variable [39]. In studies that compare index (individuals identified by pulmonary impairment) and non-index cases (individuals identified by family studies), many non-index ZZ subjects show normal lung function [45] and a survival similar to the normal population [43] if they are non-smokers. The effect of the ZZ genotype in increasing the risk of lung function impairment is likely to be overestimated due to selection bias. It is possible that other genetic factors influence the clinical course in ZZ homozygotes. It has recently been suggested that polymorphisms in the endothelial nitric oxide synthase (NOS3) gene contribute to the development of COPD in ZZ individuals [46].

Intermediate alpha-1-antitrypsin deficiency

Numerous studies have sought to establish an association between COPD and intermediate AAT deficiency. The most common causes of intermediate deficiency are the MS and MZ genotypes, present in Caucasian populations in a proportion of ~10% and 3% respectively. MM individuals have normal AAT levels, whereas MS and MZ heterozygotes have reductions in AAT levels to ~80% and 60% of normal respectively. SZ compound heterozygotes are rare but have levels even lower at ~40% of normal. SZ heterozygotes may be at increased risk for COPD if they are smokers [47], although in a recent study from Spain no association between SZ phenotype and COPD was found [48].

The results of many case-control studies have shown an increased prevalence of MZ heterozygotes in COPD patients vs. controls [9, 49–57]. The odds ratio (OR) for MZ in these studies typically ranges from 1.5–5.0. However, in many studies the controls were not selected from the same population as the cases and the results were not adjusted for confounding variables such as smoking history and age. Investigators have also assessed the risk of the MZ genotype by studying lung function in the general population [58–65]. In these studies a population sample is phenotyped for AAT variants, and the prevalence of COPD in those with the MZ phenotype is compared with the prevalence in those with the MM phenotype. Many of these studies were based on small numbers of individuals and were inadequate to detect an effect of the MZ or MS phenotype. In a recent large cohort study from Denmark there was increased risk of obstructive pulmonary disease, as determined by hospital discharge diagnosis of either asthma, chronic bronchitis or emphysema, in MZ heterozygotes (RR = 2.2) [66]. However, only first-degree relatives of ZZ COPD patients had a significantly increased risk, suggesting that other genetic or environmental factors were contributing to the increased risk in these patients. Overall, the evidence suggests that the contribution of MZ heterozygosity to the development of COPD is minor.

Polymorphisms of α_1-antitrypsin not associated with deficiency

There are several polymorphisms of the AAT gene that are not associated with AAT deficiency. For example, a polymorphism in the 3' region of the AAT gene has been associated with COPD in some populations [67, 68] but not others [57, 69, 70]. *In vitro*, this polymorphism has been associated with decreased binding of a transcription factor and decreased gene expression [71]. The most likely transcription factor is nuclear factor of IL-6 (NF-IL6 or C/EBP), which is activated by IL-6 and is known to increase expression of AAT [72]. Thus, the 3' mutation could affect the acute phase response, resulting in reduced up-regulation of AAT synthesis when inflammation is present. However, in contrast to the *in vitro* data, the 3' polymorphism was not associated with a reduced AAT acute phase response in patients undergoing open heart surgery [73] or in patients who had cystic fibrosis [74]. Thus the role of the 3' polymorphism in the pathogenesis of COPD remains unclear.

Another polymorphism in the 3' region of the AAT gene has been associated with COPD [75]. The polymorphism was also associated with normal AAT levels and was found in 8 out of 70 COPD patients but in none of 52 controls.

Other antiprotease genes

The association of emphysema with genetic defects in AAT prompted a search for genetic abnormalities of other proteases and antiproteases that may be involved in lung destruction. Alpha-1-antichymotrypsin (AACT) is another protease inhibitor which is secreted by the liver and alveolar macrophages. Several polymorphisms have been associated with COPD [76, 77], whereas other investigators have found no association [70, 78].

Alpha-2-macroglobulin (A2M) is a broad-spectrum protease inhibitor which is also synthesised in hepatocytes and in alveolar macrophages. Several polymorphisms of the A2M gene have been described [79].

Overall, these polymorphisms are rare and the evidence that they contribute to susceptibility to COPD is weak.

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) comprise a structurally and functionally related family of at least 20 proteolytic enzymes which play an essential role in tissue remodelling and repair associated with development and inflammation [80]. MMP genes have been mapped to chromosomes 11, 14, 16, 20 and 22, several of them being clustered within the long arm of chromosome 11 [81]. Overexpression of metalloproteinases has been associ-

ated with several pathological conditions, including irreversible degradation of tissues in arthritis [82, 83] and degradation of collagens in tumour invasion and metastasis, leading to poorer prognosis in patients with higher expression of MMP's [84, 85]. Several studies in animals and humans have provided evidence that MMP-1 (interstitial collagenase), MMP-12 (human macrophage elastase) and MMP-9 (gelatinase B) are important in airway inflammation and the development of emphysema. In 1992, D'Armiento et al. demonstrated that transgenic mice overexpressing human MMP-1 in the lungs developed morphological changes strikingly similar to human pulmonary emphysema [86]. Compared to wild type mice, MMP-12 knockout mice did not develop emphysema following exposure to cigarette smoke [87], suggesting that the presence of MMP-12 is critical in smoke-induced lung injury. Smokers with airway obstruction show increased expression of MMP-1 and MMP-9 compared to smokers without COPD and non-smokers [88]. Several promoter polymorphisms in MMP genes are known to alter gene expression [89–92]. A recent study found that haplotypes consisting of alleles from the MMP1 G-1607 GG and MMP12 Asn357Ser polymorphisms were associated with rate of decline of lung function ($p = 0.0007$). The data suggest that polymorphisms in the MMP1 and MMP12, but not MMP9, genes are either causative factors in smoking-related lung injury or are in linkage disequilibrium with causative polymorphisms [93].

Xenobiotic metabolising enzymes

Both the proteolytic process in the lung parenchyma and fibrotic narrowing of the small airways are in response to toxic substances contained within cigarette smoke. Genetic variation in the metabolism and detoxification of noxious substances such as hydrocarbons, epoxides and oxidants could be important determinants of host response.

Microsomal epoxide hydrolase

Microsomal epoxide hydrolase (EPHX) is an enzyme which plays an important role in the lung's ability to metabolise highly reactive epoxide intermediates which may be formed in cigarette smoke and lead to lung injury. EPHX is expressed in a variety of different cell types, including hepatocytes and bronchial epithelial cells. Two common polymorphisms occur in the EPHX gene: in exon 3 (resulting in the Tyr113→His amino acid substitution) and exon 4 (resulting in the His139→Arg amino acid substitution). The polymorphisms correlated with the level of EPHX enzymatic activity in transfected cell lines [94] but not in liver tissue samples [95]. The slow metabolizing form of EPHX was found in a higher proportion of patients with emphysema (22%) and COPD (19%) than in control subjects (6%), giving an odds ratio of ~5 [96]. In a smaller Japanese study, the slow-metabolising form of EPHX was associated with more severe COPD [97]. These results were not confirmed in a Korean population [98]. A recent study found EPHX genotypes to be associated with rate of decline of lung function in smokers [57].

Glutathione S-transferases

Glutathione S-transferases (GSTs) are members of a family of enzymes which play an important role in detoxifying various aromatic hydrocarbons found in cigarette smoke. GSTs conjugate electrophilic substrates with glutathione and this facilitates further metabolism and excretion. GSTM1 is expressed in the liver and the lung. Homozygous deletion of the GSTM1 gene occurs in approximately 50% of Caucasians. Homozygous deficiency for GSTM1 was associated with emphysema in patients who had lung cancer (OR = 2.1) [99] and severe chronic bronchitis in heavy smokers (OR = 2.8) [100]. However, in a Korean study there was no association between GSTM1 and GSTT1 polymorphisms and COPD [98].

GSTP1 is expressed in the same cell types as GSTM1, although at a higher level [101]. There is a polymorphism at position 105 (Ile105→Val), resulting in increased catalytic activity of the enzyme in vitro [102]. Homozygotes for the isoleucine allele were significantly increased in Japanese patients with COPD compared with controls (OR = 3.5) [103].

Cytochrome P4501A1

Cytochrome P4501A1 (CYP1A1) also metabolises xenobiotic compounds to enable them to be excreted. CYP1A1 is found throughout the lung and may play a role in the activation of procarcinogens. A mutation in exon 7 of CYP1A1 causes an amino acid substitution (Ile^{462}→Val) which results in increased CYP1A1 activity *in vivo* [104]. The high-activity allele (Val^{462}) was associated with susceptibility to centriacinar emphysema in patients who had lung cancer (OR = 2.5) [105].

Antioxidants

Heme oxygenase-1

Heme oxygenase degrades heme to biliverdin and has been shown to provide cellular protection against heme and non-heme-mediated oxidant injury [106, 107]. A microsatellite polymorphism within the gene promoter has been associated with pulmonary emphysema in Japanese smokers [108]. The authors furnish evidence that a larger size of the dinucleotide repeat reduces the inducibility of the enzyme, thus providing less antioxidant protection against cigarette smoke. These results have not yet been reproduced in subjects of different ethnic origins.

Inflammatory mediators

Vitamin D-binding protein

Vitamin D-binding protein (VDBP) is a 55 kDa protein secreted by the liver which is able to bind vitamin D, extracellular actin and endo-

toxin. VDBP enhances the chemotactic activity of C5a and C5a des-Arg for neutrophils by one to two orders of magnitude [109]. In addition, VDBP is known to undergo conversion to a potent macrophage-activating factor [110]. Thus, besides its vitamin D-binding function, VDBP could have important influences on the intensity of the inflammatory reaction.

There are three major isoforms of this protein, named 1S, 1F and 2, due to two common substitutions in exon 11 of the gene. Individuals who had one or two copies of allele 2 were shown to be protected against COPD [111, 112]. In addition, Horne et al were able to show a significantly increased risk of developing COPD for 1F homozygous individuals [111]. Ishii et al. confirmed this result in a Japanese population [113]. In a recent study no association was found between this genotype and accelerated decline of lung function [57]. Schellenberg et al. investigated whether the associations of VDBP isoforms with COPD could be due to the effect of VDBP on neutrophil chemotaxis [112]. However, there were no significant differences between the three VDBP isoforms in their ability to enhance chemotaxis of neutrophils to C5a. Another possible mechanism for the association with COPD is activation of macrophages at the sites of inflammation. To date, no investigators have considered the influence of these genetic variants on the protein's ability to act as a macrophage-activating factor.

Tumour necrosis factor α

Tumor necrosis factor α (TNFα) and TNFβ (lymphotoxin) are pro-inflammatory cytokines having many effects which may be important in the pathogenesis of COPD, e.g. neutrophil release from the bone marrow and neutrophil activation. The TNFα and TNFβ genes contain several polymorphisms, including a G→A transition in the TNFα gene promoter (TNFα G-308A) and an A→G transition in the first intron of the TNFβ gene (TNFβ A252G). These polymorphisms have been shown to be associated with the level of TNFα and TNFβ production *in vitro* [114]. In addition, the TNFα -308A allele has been associated with several diseases, including cerebral malaria [115] and asthma [116, 117]. An association between the TNFα -308A allele and COPD was recently found in a Taiwanese population [118]. The patients were selected on the basis of presence of chronic bronchitis and impaired lung function (FEV_1 <80% predicted and FEV_1/FVC<69%). The prevalence of the TNFα -308A allele was greatly increased in the patients vs. controls, yielding an odds ratio of 11.1 for chronic bronchitis. These results were confirmed in a Japanese population [119], whereas three other studies in Japanese and Caucasians found no association [57, 120, 121].

IL-1 complex

The IL-1 family consists of two pro-inflammatory cytokines, IL-1α and IL-1β, and a naturally occurring anti-inflammatory agent, the IL-1 receptor antagonist (IL1RN). The two forms of IL-1 are the products of different genes, but they are structurally related and bind to the same receptor. They are synthesised by a variety of cell types, including monocytes and macrophages. IL1RN is a 16-18 kD protein that binds to the IL-1 receptor with the same affinity as IL-1, but it does not possess agonist activity and therefore acts as a competitive inhibitor of IL-1 [122]. The genes of the IL-1 complex map to the long arm of chromosome 2 [123] and each of the genes is polymorphic. The IL-1 beta gene (IL1B) has a single nucleotide polymorphism in the promoter region (C-511T) [124] and the IL1RN gene has a pentaallelic polymorphic site in intron 2, containing 2–6 tandem repeats of an 86bp sequence [125]. There is evidence that allele 2 of the IL1RN gene is associated with increased susceptibility or a more severe outcome in chronic inflammatory diseases such as ulcerative colitis, systemic lupus erythematosus and alopecia areata [126–130]. The IL1B C-511T has been associated with inflammatory bowel disease [131] as well as plasma levels of IL1B and IL1RN [132].

A recent study found that IL-1 genotypes were not associated with rate of decline of lung function in smokers; however, the authors were able to demonstrate a significant influence of IL1RN / IL1B haplotypes in these individuals [133]. A smaller study in a Japanese population found no association of IL1B and IL1RN polymorphisms with COPD [134].

Mucociliary clearance

Cystic fibrosis transmembrane regulator

The cystic fibrosis transmembrane conductance regulator (CFTR) forms a chloride channel at the apical surface of airway epithelial cells and is involved in the control of airway secretions. In 1989, mutations in the CFTR gene were identified as the cause of cystic fibrosis (CF). CF carriers may also be predisposed to respiratory disease. CF heterozygotes had increased bronchial reactivity to methacholine [135] and increased incidence of wheeze accompanied by decreased FEV_1 and FEF_{25-75} [136].

The most frequent CF-causing variant is ΔF508, and heterozygosity for this mutation was increased in patients with disseminated bronchiectasis [137, 138] and in patients with 'bronchial hypersecretion' [139]. The prevalence of ΔF508 was not increased in patients with chronic bronchitis [138]. Other CFTR mutations were increased in patients with disseminated bronchiectasis and normal sweat chloride levels [140, 141]. One of these mutations is a variable length thymine repeat in intron 8 of the CFTR gene (IVS8). The IVS8-5T allele results in reduced CFTR gene expression. Studies of IVS8-5T as a risk factor for COPD have

yielded conflicting results [140, 141]. Most recently, patients with obstructive lung diseases have been screened for variants in the whole CFTR coding region [142]. The study compared 12 COPD patients with 52 controls, both groups from a Greek population. There was no statistically significant increase in CF-causing mutations in the patients versus the controls. The frequency of the Met allele of the Met470Val polymorphism was increased in the patients (71%) compared with the controls (36%).

In summary, CFTR variants were consistently associated with disseminated bronchiectasis. This may be due to the effect of these variants on the rate of mucociliary clearance. However, it is not clear whether the patients who have disseminated bronchiectasis represent a clinically distinct group or have mild, undiagnosed CF with an unknown CFTR mutation on their other chromosome [143]. In addition, all the studies described above were based on small numbers of subjects and only three [140–142] compared cases with controls. The other studies merely compared frequencies in the cases with published allele frequencies and thus the results of these studies are far from definitive.

Airway hyperresponsiveness

Beta-adrenergic receptor

Airway hyperresponsiveness (AHR) is a known risk factor for the respiratory symptoms of COPD. Polymorphisms in the β_2-adrenergic receptor (ADRB2) have previously been shown to be associated with asthma severity [144, 145], AHR [146, 147], bronchodilator response [148, 149] and level of lung function [150] (reviewed in [151]). The Arg16→Gly and Gln27→Glu polymorphisms in the ADRB2 are known to affect agonist-induced receptor downregulation *in vitro* [152, 153] and *in vivo* [154]. Joos et al. investigated the association of the common polymorphisms with rate of decline of lung function in smokers. There was a significant negative association between heterozygosity at position 27 and a rapid decline in lung function (adjusted odds ratio = 0.59, 95% CI = 0.40–0.85, p = 0.005), suggesting a protective effect of this genotype. The polymorphism at position 16 did not contribute to the rate of decline of lung function, measures of airway responsiveness or bronchodilator response in smokers [155].

Conclusion

Although there is clear evidence of a genetic contribution to the pathogenesis of COPD, few specific genes have been implicated. The major difficulty has been the lack of large-scale family and sib-pair studies using the modern technique of genome wide screening. Most studies have been case-control candidate gene studies with their known limitations. They were confined to known biologically plausible candidates, were usually too small in size to be powerful enough to detect genes of small effect and were potentially flawed by population admixture.

COPD is a result of a complex interaction between genetic and environmental factors. However, studies of the genetics of COPD have rarely included a specific investigation of this interaction [156]. The obvious environmental factor for COPD is cigarette smoking, but others could include childhood respiratory infections and air pollution. Investigation of gene-environment interactions could lead to important insights into the pathogenesis of COPD. Inclusion of gene-environment interaction terms in a genetic model may reflect the mode of action of risk factors more closely and thus add power to genetic association studies of COPD.

In the future, more information about the role of genetic risk factors in the development of COPD will be provided by large-scale family studies, genome wide association studies using single nucleotide polymorphisms and investigation of an increased number of possible candidate genes identified by the Human Genome Project.

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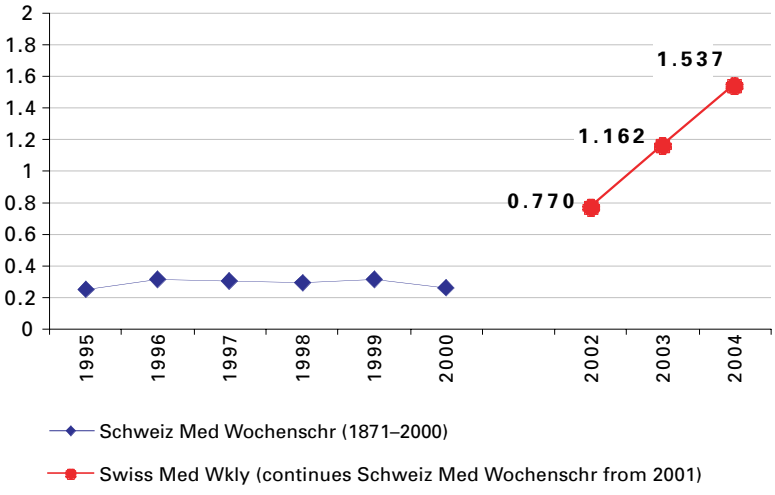

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