The pathogenesis of COPD is believed to result from 3 major pathways: (a) protease-antiprotease imbalance, (b) oxidative stress and (c) dysregulation of tissue homeostasis within the lung. These pathways have been assessed by many studies in cell models of disease, animals and in ex vivo samples. However cell and animal models may not reflect human disease and ex vivo samples are usually from individuals with established lung disease. There is also concern that the examination of small numbers of samples may not capture the heterogeneity of COPD, for example those with airways disease rather than emphysema, the frequent or no exacerbation group and those with disease progression compared with individuals who are stable. The complexity increases further when trying to stratify by systemic inflammation, co-morbidities and the effects of inhaled and oral therapy. One way to address these concerns is to use genetic studies to identify genes that are important in individuals who have developed COPD. Genetic polymorphisms do not change throughout life and can be readily identified using modern sequencing technology. Clustering of functional polymorphisms in individuals with disease can identify pathways that are important in the development of components of the COPD phenotype. These pathways can be used to inform mechanistic studies and to stratify subjects to receive the most appropriate therapy.

The best-understood example of genetically induced emphysema results from mutations in the α₁-antitrypsin gene (SERPINA1). Ninety-five percent of severe deficiency of α₁-antitrypsin results from the Z allele (Glu342Lys; denoted PIZZ in the homozygote) that causes newly synthesized protein to polymerize and be retained within hepatocytes1,2. These polymers form the Periodic Acid Schiff (PAS) positive, diastase-resistant inclusions that are present in all individuals with a Z allele and are associated with neonatal hepatitis, cirrhosis and hepatocellular carcinoma. The concomitant lack of circulating α₁-antitrypsin predisposes the α₁-antitrypsin homozygote to early onset emphysema. It appears that even a single allele of Z α₁-antitrypsin may increase the risk of COPD3,4.

ASSOCIATION STUDIES IN INDIVIDUALS WITH COPD

There are many association studies that have assessed genes that may predispose smokers to COPD. Ideally these studies include two populations matched for all factors that are known to affect FEV₁ (age, sex, smoking history, occupational exposure to dusts, α₁-antitrypsin deficiency and bronchial hyper-reactivity) but one group has irreversible airflow obstruction and the other group is unaffected. Such studies are often complicated by small numbers of patients and the difficulty in matching for all known environmental and genetic factors that predispose to COPD. It is made more difficult as some of these factors have not yet to be determined. Moreover COPD is a heterogeneous disease and it seems likely that the genes that are responsible for the progression of small airways disease are different from those that predispose smokers to emphysema3. Finally researchers can only assess genes that have already been described where they think it is biologically plausible that mutations in the protein may be associated with COPD. The candidate gene approach is straightforward however the limitations, particularly the risk of selection bias, means that the results need to be interpreted with caution. The studies provide good evidence of a link between the following genes and COPD: microsomal epoxide hydrolase, glutathione S-transferase, haem oxygenase-1, superoxide dismutase 3, TGF-beta and matrix metalloproteinase (MMP)-126.
GENETIC FACTORS IDENTIFIED FROM GENOME WIDE ASSOCIATION STUDIES (GWAS)

Genome wide studies use the power of genomic analysis and computational technology to assign polymorphisms throughout the genome with disease. SNPs in chromosome 15 at the α-nicotinic acetylcholine receptor CHRNA3/5 locus were found to reach genome-wide significance in individuals with COPD and have subsequently been replicated in several independent studies. This locus is significantly associated with pack-years of smoking, emphysema (by CT scan) and airflow obstruction. The C allele of the rs8034191 SNP has a population attributable risk for COPD of 12.2% and has previously been identified in genome–wide association studies of lung cancer. Individuals who carry this SNP may require more cigarettes to satisfy nicotine addiction, may inhale more deeply and may find it more difficult to withdraw from cigarette smoking. Indeed, it has been reported that the association of the CHRNA3/5 locus is substantially mediated by smoking phenotype, although this finding has been disputed. Tissue specificity of the alpha 1-antitrypsin deficiency. However none of the newly identified genes have to date no genes that control antiproteases have been robustly associated with COPD in GWAS analysis. Taken together these studies are starting to define new molecular pathways associated with COPD, as is most evident in individuals with α1-antitrypsin deficiency. However none of the newly identified genes have proved effective in identifying individuals with progressive disease. This may in part be explained by the many different ways of developing this phenotype.

GWAS have also identified a locus at 4q22.1 containing the gene FAH/M13A to be significantly associated with COPD and lung function in multiple cohorts; the function of FAM13A is unclear. The hedgehog interacting protein (HHIP) at 4q31 was identified and replicated by GWAS as being associated with both COPD and lung function. It appears to play a role in signaling that modulates lung development or remodeling. HHIP is expressed in pulmonary tissues but at lower levels in COPD-affected lungs, and disease-associated SNPs have been identified within the gene’s promoter (rs6537296A and rs1542725C) that appear to reduce its transcription. To date no genes that control proteases or antiproteases have been robustly associated with COPD in GWAS analysis.

Taken together these studies are starting to define new molecular pathways associated with COPD, as is most evident in individuals with α1-antitrypsin deficiency. However none of the newly identified genes have proved effective in identifying individuals with progressive disease. This may in part be explained by the many different ways of developing this phenotype.

References


