Genetic predisposition to accelerated decline of lung function in COPD

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Abstract: Environmental exposures and genetic susceptibility can contribute to lung function decline in chronic obstructive pulmonary disease (COPD). The environmental factors are better known than the genetic factors. One of the commonest reasons of accelerated forced expiratory volume in one second (FEV_1) decline in COPD is the continuation of the smoking habit. In addition, COPD patients have frequent acute respiratory infections which can also accelerate the decline of FEV_1. All of the gene variants that have been reported in association with accelerated decline of lung function in COPD represent advancement because the findings generate plausible hypotheses about the possible mechanisms by which gene products could accelerate or avert FEV_1 decline. Unfortunately, the results have not been consistently replicated and, animal models required to functionally assess the genetic findings, have not yet yielded sufficient data. Genome-wide association studies should provide more definitive results in COPD and other multigenic conditions. Until these studies are reported, the data to date suggest that products encoded by the alpha-1 antitrypsin, some matrix metalloproteinases, and a number of antioxidant genes are associated with accelerated FEV_1 decline in COPD. Data on gene variants associated with acute exacerbations of COPD are now emerging.

Keywords: lung function, COPD, Smoking, genes

The Lung Health Study enrolled 5887 participants with mild-to-moderate chronic obstructive pulmonary disease (COPD) in a 5-year study to evaluate the effects of smoking cessation and maintenance therapy with inhaled ipratropium on the annual change in lung function (Anthonisen et al 1994). Large reductions in smoking amount (of up to 50%) had no observable effect on the decline in forced expiratory volume in one second (FEV_1). Instead, participants in the Lung Health Study who quit smoking and remained abstinent (sustained quitters) exhibited a significant increase in FEV_1 during the 1st year after smoking cessation, followed by a steady decline comparable with that reported for never-smokers (Anthonisen et al 2002). Among smokers who achieved intermittent periods of complete smoking abstinence but at other times maintained their regular smoking habit (intermittent quitters), the annual rate of decline in FEV_1 was intermediate between that of sustained quitters and continuing smokers who did not have periods of abstinence. Healthcare providers should continue to emphasize that complete smoking cessation is the best approach to obtain a beneficial effect in pulmonary function (Simmons et al 2005). In addition, prevention of acute exacerbations of COPD (AECOPD)—through appropriate vaccinations (Bateman et al 2004) and combined treatment with long-acting bronchodilators (LABA) and inhaled corticosteroids (ICS) (Soriano et al 2003; Szafranski et al 2003)—is also important as AECOPD can provoke steeper decline of FEV_1 over time, albeit such decline is less pronounced in sustained quitters than in smokers (Kanner et al 2001; Wilkinson et al 2003).

The mechanisms through which cigarette smoking and AECOPD accelerate FEV_1 deterioration are complex, but a predominant mechanism is the increased oxidative

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stress in the airways (Nagai et al 2006; Rytila et al 2006; Yigla et al 2006). Oxidative stress induces transcription in a number of antioxidant genes such as the glutathione S-transferase (GST) (ie, GSTM1, GSTT1, and GSTP1), heme oxygenase (HMOX)-1, and microsomal epoxide hydrolase (mEPHX). Yet in some subjects, these genes present polymorphisms that are associated to accelerated decline of lung function. A gene promoter polymorphism (characterized by >33 repeats) in HMOX-1 is associated with steeper mean FEV_1 decline (62 ml/year) in heavy smokers (Guenegou et al 2006) in accordance with previously reported findings (Yamada et al 2000). An association between rapid decline of mean FEV_1 (approximately 150 ml/year) and the presence of all three GST polymorphisms (GSTM1, GSTT1, and GSTP1) in smokers from the Lung Health Study has also been described (He et al 2002). It has also been reported that the proportion of individuals with innately slow mEPHX activity was significantly higher in patients with COPD (Koyama and Geddes 1998) and that a coding variant in codon 113 (exon 3) of mEPHX is associated with COPD and rapid FEV_1 decline (Smith and Harrison 1997; Sandford et al 2001; Xaio et al 2004). Thus, defective antioxidant defense mechanisms may in fact be responsible for the steeper decline of FEV_1 in a number of COPD patients.

Hereditary emphysema due to reduced alpha -1-antitrypsin (A1AT) deficiency (PiZZ homozygotes) is the primary example of a proven genetic factor predisposing to accelerated lung function decline in a particularly disparate phenotype (DeMeo and Silverman 2004). However, only a small number of cigarette-induced COPD patients may have under-diagnosed A1AT deficiency as the main cause of their airflow obstruction and other pathophysiological mechanisms appear to be more important (Molfino 2004). For example, COPD sufferers with a rapid decline in mean FEV_1 (>150 ml/year) exhibited an association with the PiMZ genotype of the A1AT gene only when a family history of COPD was present (Yamada et al 2000). This suggests that additional factors to the A1AT genotype may contribute to the fast decline of lung function (Sandford et al 2001). Moreover, patients with A1AT deficiency have been shown to have an increased frequency of the GSTP1 105Val polymorphism which impairs its antioxidant enzymatic activity (Rodriguez et al 2005). Other factors that may provoke enzymatic degradation of the extracellular matrix, leading to emphysema and airflow limitation, include polymorphisms of the matrix metalloproteinases (MMPs) 1 and 12 genes which have been reported in association with rapid rate of decline of lung function in COPD (Joos et al 2002).

At the 11th year of follow-up, the Lung Health study results show that airway hyperresponsiveness to metacholine, but not the FEV_1 response to the $ß_2$-agonist isoproterenol predicts the rate of decline of FEV_1 in COPD (Anthonisen et al 2005). This seems to be the long-term clinical confirmation of a previous report (Joos et al 2003) in the same patient population that $ß_2$-adrenoceptor polymorphisms may not be associated to the rate of FEV_1 decline. In such previous study (Joos et al 2003), however, there was a significant ($p = 0.0007$) negative association between heterozygosity at position Gln27 of the $ß_2$-adrenoceptor and rapid decline in lung function suggesting that heterozygosity at position 27 may be protective against an accelerated rate of decline in lung function in Caucasians.

Taken together, the above results suggest that gene variants which incline the balance towards enhanced enzymatic degradation of the lung parenchyma and towards increased airway hyperresponsiveness appear to contribute to the accelerated lung function decline in COPD (Yamada et al 2000; DeMeo and Silverman 2004; Molfino 2004; Xiao et al 2004).

Since exacerbations play such an important role in FEV_1 decline (Donaldson et al 2002), it may be important to find out if there is a genetic predisposition to AECOPD. In this regard, it has recently been reported that a SNP in the inflammatory chemokine CCL1 gene encoding for a leukocyte chemoattractant is associated with an increased incidence of AECOPD in patients of Japanese origin (Takabatake et al 2006). Finally, genome-wide RNA interference screening to identify host factors required for infections is now possible and it is hoped that this technique would allow the identification of other genetic factors associated with AECOPD (Agaisse et al 2005).

In summary, complete smoking cessation continues to be the best nonpharmacological approach to deter the rentless decline of lung function in COPD and, polymorphisms in antioxidant, A1AT, and MMPs genes, seem associated with fast FEV_1 decline. There may be gene–gene and gene–environment interactions that favor steeper lung function declines, but data are just emerging.

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