LETTERS

Association between the *IL6*-174G/C SNP and maximally attained lung function

Recently, He *et al*[1] reported that the C allele of the interleukin 6 (*IL6*)-174G/C promoter polymorphism was associated with a rapid decline in forced expiratory volume in 1 s (FEV_1) (≥3% predicted/year) and susceptibility to chronic obstructive pulmonary disease (COPD) in middle-aged smokers derived from three different cohorts.[1] Alternatively, as also suggested by He *et al* in their discussion,[1] we hypothesised that the *IL6*-174G/C single nucleotide polymorphism (SNP) might not only affect the rate of lung function decline but also the maximally attainable value at around the age of 25. We investigated this hypothesis in young adults recruited from the East Flanders Prospective Twin Survey. Reproducible prebronchodilator lung function measurements according to international standards[2] and *IL6*-174G/C genotypes were available of 427 individuals (mean age 24.6±4.5 (SD), 232 women and 195 men). Mean FEV_1, forced vital capacity (FVC) and FEV_1/FVC ratio did not differ between current (n=131), former (n=33) and never smokers (n=263). The *IL6*-174G/C SNP was genotyped using pyrosequencing technology. PCR conditions and primer sequences are listed in online table 1. Genotype frequencies of the *IL6*-174G/C SNP were in accordance with Hardy–Weinberg equilibrium (p>0.05) (online Table 2). Data were analysed using the PROC MIXED method as previously described.[3]

In this sample of young adults, the *IL6*-174G/C SNP showed no association with the FEV_1, but the C allele of the *IL6*-174G/C SNP was significantly associated with a lower FVC (p=0.03) and a higher FEV_1/FVC ratio (p=0.003) under an additive mode of inheritance and independent of smoking status and birth weight (table 1).

Our results are in line with animal and in vitro studies consistently showing that IL-6 promotes lung morphogenesis, lung branching and surfactant protein A production during intrauterine lung development.[4] Local IL-6[4] and IL-6 receptor[5] expression has been described in the lungs during fetal development. Accordingly, our data suggest that the *IL6*-174G/C SNP may alter local IL-6 expression levels, potentially interfering with normal lung maturation. Collectively, the study by He *et al*[1] combined with these findings suggest that an interesting next step could be to investigate local IL-6 expression in the lungs in relation to the *IL6*-174G/C SNP during the course of life: during intrauterine development, at young adult age, and in middle-aged non-smokers versus smokers with and without COPD.

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Table 1 Descriptive data and associations between lung function and the *IL6*-174G/C single nucleotide polymorphism

	IL6-174G/C				
	GG	GC	CC	β (SE)	p Value adjusted for birth weight
n	143	197	87		
Age (years)	24.5 (0.4)	24.3 (0.3)	25.3 (0.5)		
Sex (M/F)	70/73	83/114	42/45		
Traits					
FEV_1 (% predicted)*	101.2 (1.1)	103.2 (1.0)	100.3 (1.1)	−0.19 (0.95)	0.839
FVC (% predicted)*	106.4 (1.1)	105.2 (1.0)	100.9 (1.3)	−2.18 (1.02)	**0.034**
FEV_1/FVC	82.2 (0.7)	84.8 (0.6)	86.1 (0.7)	1.83 (0.61)	**0.003**

Data are mean (SE).
*The percentage predicted values were calculated according to reference equations.[2]
F, female; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; M, male.

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Authors' reply

van den Borst and colleagues present interesting data regarding the role of the interleukin 6 (IL6)-74G/C promoter polymorphism (rs1800795) in determining the level of lung function.[1] We have shown that the C allele of the -174 polymorphism was associated with more rapid decline of lung function in the Lung Health Study (LHS) and with chronic obstructive pulmonary disease in the National Emphysema Treatment Trial (NETT).[2] However, there was no association of this polymorphism with baseline lung function in the LHS, and we hypothesised that this may have been due to the younger age of the participants of the LHS compared with the NETT group. Specifically, the baseline lung function in the LHS participants may have been strongly influenced by the maximal attained lung function, whereas lung function in the NETT group (on average two decades older) may be more reflective of the rate of decline of lung function. In this model, the -174G/C polymorphism primarily affects the rate of decline of lung function in response to cigarette smoke and not the maximal level attained during development.

The data from van den Borst *et al* show an association of the -174C allele with lower forced vital capacity in young adults who were on average 23 years younger than the LHS cohort which we studied. Thus, their results are more reflective of the effect of this polymorphism during lung development than ours, and this may partly explain the differences in results with regard to baseline lung function values. However, we agree with van den Borst and colleagues that further studies are warranted to clarify the mechanism underlying these observations.

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