Table 1 Decline in FEV_1 (ml/year) in non-smoking asthmatics and controls in different putative IL-1 haplotypes

IL-1 haplotype	(1) IL1RN A2/ IL1B –511T	(2) IL1RN A2/ IL1B –511C	(3) IL1RN A1/ IL1B –511T	(4) IL1RN A1/ IL1B –511C	p value*	Post hoc tests between allele groups†
Non-smoking controls (n=124)	41.8 (13.8) (n=54)	44.8 (12.3) (n=32)	50.7 (11.2) (n=7)	45.5 (19.4) (n=31)	0.27	Not tested
Non-smoking new asthma cases (n=40)	63.2 (24.6) (n=18)	37.7 (20.7) (n=4)	30.9 (16.9) (n=4)	51.0 (24.8) (n=14)	0.0443	3<1, p=0.02 2<1, p=0.06

*Two way analysis of variance; †LSD test of means.

the same methods in adult incident non-smoking asthmatic patients and non-smoking controls. Our results indicate that the association of IL-1 genetics with rate of decline in lung function is not limited to smokers.

New adult asthma cases and controls were selected from a cohort of the Mini-Finland Health Survey (MFHS) and later re-evaluated. A more detailed description of the methods used in MFHS has been published elsewhere.[2] The accuracy of the method of asthma case ascertainment has also recently been described.[3] IL-1 haplotypes were found to be significantly associated with the rate of decline of lung function in non-smoking incident cases of asthma (new asthma during follow up) but not in controls (table 1). Of the individual haplotypes, Joos *et al* found that *IL1RN A1/IL1B –511T* was associated with a rapid decline of lung function in smokers and *IL1RN A2/IL1B –511T* with a slow decline. In our control group the observed differences were not significant. Surprisingly, in the asthma group the haplotypes had the opposite effects from those in smokers: *IL1RN A1/IL1B –511T* was associated with a slower decline in lung function and *IL1RN A2/IL1B –511T* with a more rapid decline. *IL1RN A2/IL1B –511T* has previously been found to be associated with many inflammatory diseases.[4] The function of these haplotypes would therefore appear to be disease specific.

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Authors' reply

Karajalainen and colleagues present interesting data on the relationship of IL-1β and IL-1 receptor antagonist haplotypes and the rate of decline of lung function in incident asthmatic subjects in a Finnish cohort. We reported that the *IL1RN A1/IL1B –511T* haplotype was associated with a more rapid decline in lung function in smokers in the Lung Health Study; in contrast, they found that this same haplotype was associated with a slower rate of decline in lung function in patients with asthma. The authors suggest that this apparent contradiction may be because the function of these haplotypes is disease specific. We agree that a different effect of the same haplotype could occur because of fundamental differences in the pathophysiological processes which cause airflow obstruction in asthma and chronic obstructive pulmonary disease (COPD). In asthma, CD4+ Th2 cells underlie persistent eosinophilic inflammation and remodelling in medium sized and larger airways. In COPD, neutrophils and CD8+ cells appear to play an important role in the airflow limitation by causing proteolytic destruction of peripheral lung parenchyma and fibrous scarring of the small membranous and respiratory bronchioles. Although inflammation appears to be central to both processes, the roles of IL-1β and of IL-1 receptor antagonist in these conditions is unknown and it is possible that the polymorphisms that are responsible for this haplotype could have opposite effects.

Alternatively, these apparently contradictory results could be due to different genetic histories of the two study groups. Our study group was taken from the white population in the United States whereas Karjalainen *et al* studied Finnish individuals. It may be that the polymorphisms which are typed to establish these haplotypes do not, by themselves, change the function or level of expression of the IL proteins but are in linkage disequilibrium with a causal polymorphism(s). In this case, the IL1 allelic associations could be different in different populations. The bottleneck in the genetic history of the Finnish people could have established a founder effect and resulted in the function altering allele being found on a different genetic background from that in the white population of the United States.

Whatever the correct explanation, these results support the growing evidence that genetic variation at the IL-1 locus is important in modulating the severity and/or functional consequences of a number of inflammatory conditions.

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Molecular analysis of drug resistant TB

Since the mid 1980s the number of notified cases of TB in the UK has continued to rise with the largest increases noted in London and inner city areas.[1] King George Hospital in Goodmayes, Essex provides clinical services to a population of approximately 230 000; 17% are non-white subjects including immigrants from countries with high rates of *M tuberculosis* infection and drug resistance. From September 1996 to July 1997 47 adult cases of culture proven TB were identified including seven with drug resistant isolates. None was identified by contact tracing. A previous TB audit of African born patients revealed a high rate of drug resistance (6/24 (25%)) and delays in obtaining drug sensitivities which could have been detrimental to patient management.[2]

Under these circumstances the rapid identification of drug resistance in *M tuberculosis* isolates would have been helpful. The aim of this study was to determine retrospectively the usefulness of PCR-reverse hybridisation methods for screening for mutations within or adjacent to *M tuberculosis* genes associated with rifampicin (*rpoB*) and isoniazid (*inhA, katG*, and *ahpC*) resistance. We also determined whether resistance genotyping combined with IS6110 typing could help to identify clusters of drug resistant cases not previously identified by contact tracing.

Seven consecutive drug resistant *M tuberculosis* culture isolates were analysed for rifampicin and isoniazid resistance and the results were compared with conventional susceptibility testing. The commercially available

Table 1 Demographic data, site, phenotypic and genotypic resistance of the seven resistant study isolates

Isolate	Age	Country of birth	Site of TB	Drug resistance	Resistance genotype	
					Isoniazid	Rifampicin
1	24	Nigeria	Pulmonary	INH/RIF	Wild type	*rpoB* mutation
2	21	Somalia	Pulmonary	INH	*katG* mutation	Wild type
3	40	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
4	17	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
5	20	Zaire	Pulmonary	INH	*inhA* mutation	Wild type
6	42	UK	Pulmonary	INH	*inhA* mutation	Wild type
7	44	Somalia	Sternum	PZ	Wild type	Wild type

INH=isoniazid; RIF=rifampicin; PZ=pyrazinamide. Isolates 3 and 5 had indistinguishable IS6110 types. Isolates 1 and 4 were not typable due to insufficient culture and the banding pattern of isolate 6 was uninterpretable.

assay INNO-LiPA Rif.TB[3] was used to detect *rpoB* mutations and an in-house PCR-reverse hybridisation line probe was used to detect mutations in or adjacent to the *katG*, *inhA*, and *ahpC* genes.[4] The isolates were also IS6110 typed.[5]

The single rifampicin and isoniazid resistant isolate had an *rpoB* gene mutation associated with rifampicin resistance (table 1). Four of the five isoniazid resistant isolates had the same single point mutation upstream of the *inhA* gene and the other a single *katG* point mutation. Isolates 3 and 5 had indistinguishable IS6110 types that could represent isolates where recent transmission had occurred. No mutations were detected in the 40 fully susceptible isolates.

PCR-reverse hybridisation methods were highly sensitive and specific at detecting mutations that predict for isoniazid and rifampicin resistance. We also demonstrated that different point mutations can be used to discriminate between isoniazid resistant isolates. We believe that with automation and the addition of oligonucleotide probes designed to detect mutations associated with pyrazinamide (*pncA*)[6] and ethambutol (*embB*)[7] resistance, a system capable of detecting resistance to four front line antituberculous drugs will soon be commercially available. Rapid resistance detection by PCR-reverse hybridisation is likely to have a major impact on patient management and our understanding of the epidemiology of drug resistant TB.

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Lung bullae and marijuana

A previous paper from this hospital described apical lung bullae in four young male marijuana smokers, three West Indian and one Caucasian.[1] Two further cases were recently reported, both in Caucasian men.[2] We describe three further cases (one woman) with large upper lobe bullae. All are Caucasian and had a prolonged history of heavy marijuana smoking with an alpha$_1$-antitrypsin level within the normal range (table). These further cases support the view that marijuana may have a causal role in the development of lung bullae. We suggest that a detailed marijuana smoking history is taken from patients of all ethnic origins with upper lobe bullae.

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Pathophysiology of COPD

The paper by Dentener *et al*[1] is interesting and contributes to the understanding of the pathophysiology of chronic obstructive pulmonary disease (COPD). It is becoming clear that COPD is a systemic syndrome, and this paper suggests some potential mechanisms. However, a number of issues merit further comment.

It is noted that, in healthy controls, there is a wide range of C reactive protein (CRP) values extending well beyond what would be considered to be the normal range. The reason for this is unclear, but it does suggest that these individuals are not as healthy as described. In addition, patients with stable COPD have a range of CRP values that also extend beyond this normal range. This is not consistent with previous studies, which suggests that, in patients with stable COPD, the range of CRP values falls within the normal range.[2] Although patients with bronchiectasis were excluded, it is possible that undiagnosed bronchiectasis may have been present. Previous work has shown that 29% of patients presenting with what appeared to be stable COPD had CT evidence of at least mild bronchiectasis.[3] This could conceivably explain a wider range of CRP levels. In addition, it is interesting that after just 5 days of treatment for an acute exacerbation of COPD the CRP had returned to a level below that of the stable cohort in the study. Since standard treatment for an exacerbation is able to achieve this in just a few days, it suggests that the stable group may have contained individuals that were in fact not so stable.

The authors allude to the potential confounding effect of systemic corticosteroids in the study. The changes in total leucocyte count during the exacerbation are likely to be due to the effect of prednisolone, making it difficult to interpret the changes in leucocyte count. In stable patients the action of corticosteroids may also confound the results. It is possible that, even in patients using inhaled corticosteroids, leucocyte numbers could be affected since there may be significant bioavailability at higher doses. Leucocyte count should therefore not be used as a marker for systemic inflammation in these patients.

Finally, it would appear that the exacerbations of COPD might have been mild, despite the presence of severe COPD on lung function criteria. Although $Paco_2$ was slightly higher and Pao_2 slightly lower than in the stable group, these differences were small in magnitude. The pH was not significantly different and, in fact, the stable group contained individuals with a lower pH (range 7.30–7.50) than in the exacerbated group (pH 7.34–7.49). Although the mean CRP level appears higher than in stable patients, the range does not differ significantly. This may therefore have led to a less profound change in inflammatory markers than might have been expected, and a study looking at more severe exacerbations may be more revealing.

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Table Characteristics at presentation of three cases of apical lung bullae in marijuana smokers

	Case 1	Case 2	Case 3
Age on presentation (years)	33	45	38
Sex	Male	Female	Male
Ethnic origin	Caucasian	Caucasian	Caucasian
Tobacco smoking history	9 pack years	10 pack years	20 pack years
Marijuana smoking history	2–3 joints/day, "heavy" 10 years	Weekends/evenings, "moderate" 10 years	0.25 oz marijuana/week, "heavy" 24 years
Alpha$_1$-antitrypsin (g/l) (normal range 1.1–2.1)	1.4	2.3	1.6
FEV_1 (l) (% predicted)	2.7 (64)	2.4 (96)	3.7 (90)
FVC (l) (% predicted)	4.3 (85)	3.3 (112)	4.7 (94)
FEV_1/FVC (%)	63	73	79
T_{LCO} (% predicted)	9.44 (81)	4.99 (62)	–
K_{CO} (% predicted)	1.44 (88)	1.10 (64)	–

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; T_{LCO}=carbon monoxide transfer factor; K_{CO}=carbon monoxide transfer coefficient.