USA. [§]Hospital Clinic, Servicio de Pneumologia, Barcelona, ^{***}University of Barcelona, Barcelona, Spain. ^{**}Hospital for Sick Children, Toronto, ON, Canada. ^{##}Dept of Respiratory Medicine, University Maastricht, Maastricht, The Netherlands. ^{††}Department of Pediatric Clinical Physiology, Queen Silvias Children's Hospital, Gothenburg, Sweden. ^{###}University Hospitals Birmingham NHS Trust, Birmingham, UK. ⁺⁺⁺University of Aarhus, Aarhus, Denmark.

STATEMENT OF INTEREST

None declared.

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Variation in the tumour necrosis factor- α gene is not associated with susceptibility to Asian COPD

To the Editors:

In a recent issue of the *European Respiratory Journal*, CHAPPELL *et al.* [1] clearly demonstrated that the lack of association with any of the tumour necrosis factor (TNF)- α single nucleotide polymorphisms or haplotypes makes it highly unlikely that polymorphisms in this gene play a major role in susceptibility to chronic obstructive pulmonary disease (COPD).

Their sample sizes were sufficient to elucidate association of TNF- α gene variations with susceptibility to COPD. However, they neglected the effect of ethnicity differences in genetic susceptibility to COPD. The frequency of the TNF- α -308*2 allele in Caucasian control populations (10–17%) is higher than that in Asians (0–8%) [1–10].

Genetic susceptibility to COPD is dependent upon the action of several gene polymorphisms, sex, age and ethnicity [2]. The TNF- α gene is known to have a polymorphic site at position -308. The TNF- α -308*2 allele, which is associated with a higher level of TNF- α production, has been associated with chronic bronchitis, a characteristic part of COPD, in a Taiwanese population [3]. However, the association of a polymorphism of TNF- α with susceptibility to COPD or to tobacco-related

airway inflammation has not yet been confirmed in Asians. It was investigated whether the TNF- α -308*2 allele was associated with COPD in a Japanese population using a PCR-based genotyping assay [4]. The TNF- α -308*2 allele was found in one (1.9%) out of 53 patients with COPD and in one (1.5%) out of 65 smoker control subjects without COPD [4]. The frequency of the major allele, *i.e.* TNF- α -308*1, in the smoker control subjects (0.99) was consistent with data reported previously for other Japanese populations, suggesting that the present samples are representative of TNF- α gene polymorphism in the Japanese population [5]. However, there were no differences between COPD patients and smoker control subjects regarding the allele and genotype frequency of TNF- α . Since chronic bronchitis is not exactly the same, in terms of definition and tobacco sensitivity, as pulmonary emphysema, which is a major feature of COPD, it is possible that the TNF- α polymorphism is associated with infection-related bronchitis rather than tobacco-smoke-related alveolar wall destruction. However, most of the TNF polymorphism studies investigating COPD susceptibility revealed negative results for various Asian populations (table 1) [6–9]. Only one group of authors have insisted that the TNF- α -308*2 may be partly associated with the extent of emphysematous changes in patients with COPD [9].

TABLE 1 Association of tumour necrosis factor (TNF)- α gene polymorphism with chronic obstructive pulmonary disease (COPD) in Asian patients in various studies

First author [Ref.]	Race	Subjects n			Gene position	TNF- α A allele frequency %			Association with COPD
		COPD	SC	PC		COPD	SC	PC	
HUANG [3]	Taiwanese	42	42	99	TNF- α -308*2	19	2.4**	5.1**	Significant
ISHII [4]	Japanese	53	65		TNF- α -308*2	1.9	1.5		NS
SAKAO [9]	Japanese	106	110	129	TNF- α -308*2	16.5	8.2**	7.8**	Significant
CHIERAKUL [6]	Thai	57	67		TNF- α -308*2	7.9	4.7 [#]		NS
JIANG [7]	Han Chinese (Beijing)	57	208		TNF- α -308	5.8	3.1 [*]		NS
HEGAB [8]	Japanese	88	61		TNF- α -308	2	0		NS

A allele: adenine allele (allele 2); SC: smoker control; PC: population control; TNF- α -308*2: position -308 on TNF- α allele 2; NS: nonsignificant. **: $p < 0.001$; [#]: $p = 0.14$; ^{*}: $p = 0.131$.

Among Caucasian data, most of the TNF- α polymorphism studies investigating COPD susceptibility have revealed negative results. However, several authors have insisted that homozygosity of this allele predisposes the patient to more severe airflow obstruction and a worse prognosis in a small number of COPD cases [10].

Thus it is necessary to study polymorphisms within the tumour necrosis factor- α gene in a large collection of well-characterised Asian chronic obstructive pulmonary disease patients and control subjects, as in the European Union collaborative project [1]. However, these collective data strongly suggest that tumour necrosis factor- α gene polymorphism does not play a major role as a genetic risk factor for chronic obstructive pulmonary disease in either Caucasian or Asian individuals. However, the tumour necrosis factor- α gene polymorphism may be associated with functional impairment or prognosis in chronic obstructive pulmonary disease.

S. Teramoto, T. Ishii, M. Ishii, H. Yamamoto, Y. Yamaguchi, S. Hibi and Y. Ouchi

Dept of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

STATEMENT OF INTEREST

None declared.

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