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Heme oxygenase-1 gene promoter polymorphism and decline in lung function in Japanese men

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation in the lung airway. Cigarette smoking is the most important risk factor for COPD.[1] Heme oxygenase-1 (HO-1) is a key enzyme in heme metabolism and provides cytoprotection against oxidants in cigarette smoke.[2] A $(GT)_n$ dinucleotide repeat in the human *HO-1* promoter shows length polymorphism which is categorised into three groups: S-allele (<27 GT repeats), M-allele (27–32 GT repeats), and L-allele (≥33 GT repeats).[3] The L-allele was found to be associated with reduced *HO-1* inducibility and susceptibility to pulmonary emphysema in a case-control study of Japanese male smokers.[3] Conversely, He *et al*[4] reported that *HO-1* polymorphism was not related to a rapid decline in lung function in a prospective study of white smokers.

To evaluate the role of *HO-1* polymorphism in the decline in lung function in Japanese subjects, 101 Japanese male ex-smokers with mild to severe COPD (forced expiratory volume in 1 second (FEV_1) 40–90% predicted and FEV_1/FVC <70%) were enrolled from January 2000 to December 2001 and *HO-1* polymorphism was checked by PCR with peripheral blood DNA. Spirometric tests were performed at the beginning of the study and annually for 3 years. All participants sustained smoking cessation and were treated with bronchodilators including β_2 agonists and/or anticholinergic agents but not the long acting anticholinergic tiotropium. Rapid decliners are defined as subjects with a mean annual decrease in FEV_1 of ≥3.0% predicted,[1] whereas non-rapid decliners were subjects with a mean annual decline in FEV_1 of <3.0% predicted. Patients with active pneumonia, bronchial asthma, and malignant disease were excluded.

There were 28 individuals with the L-allele (L-allele carriers) and 73 without the L-allele (non-L-allele carriers). The baseline characteristics of L-allele carriers and non-carriers did not differ (table 1). At the end of the follow up period there were 25 subjects with a rapid decline in lung function and 76 non-rapid decliners. The mean annual decline in FEV_1 % predicted in L-allele carriers was significantly larger than in non-carriers (mean (SE) 2.74 (1.22)% per year *v* −0.57 (0.89)% per year, p = 0.044, unpaired *t* test, table 1). The proportion of rapid decliners was significantly higher among L-allele carriers than in non-L-allele carriers (12 (42.9%) *v* 13 (17.8%), p = 0.009, χ^2 test, table 1). Furthermore, the factors associated with a rapid decline in lung function were calculated by multivariate logistic regression analysis to adjust for potential risk factors including age, smoking status (pack-years), baseline FEV_1 predicted, and L-allele carrier status. As a result, the adjusted odds ratio of L-allele carrier status for rapid decliners was 3.9 (95% CI 1.4 to 10.6), p = 0.009 (12 (48.9%) in rapid decliners *v* 16 (21.1%) in non-rapid decliners). Other factors were not significantly associated with a rapid decline in lung function.

Table 1 Mean (SE) baseline characteristics and decline in lung function in L-allele carriers and non-L-allele carriers

Characteristics	L-allele carrier (n = 28)	Non-L-allele carrier (n = 73)	p value
Age (years)	70.3 (1.7)	70.6 (0.9)	0.84*
Sex (M/F)	28/0	73/0	>0.99**
Smoking status			
No of ex-smokers	28 (100%)	73 (100%)	>0.99**
Pack-years	44.7 (4.6)	49.3 (3.6)	0.47*
Pulmonary function			
FEV_1%FVC	59.6 (1.4)	61.0 (1.0)	0.83*
FEV_1 (l)	1.41 (0.1)	1.47 (0.1)	0.69*
FEV_1 (% predicted)	62.6 (4.8)	65.7 (3.3)	0.61*
Treatment			
Smoking cessation	28 (100%)	73 (100%)	>0.99**
Bronchodilator	28 (100%)	73 (100%)	>0.99**
Complications			
Hypertension	7 (25 %)	15 (20.5%)	0.60**
Diabetes mellitus	3 (10.7%)	8 (11.0%)	>0.99**
Hyperlipidaemia	3 (10.7%)	5 (6.8%)	0.68**
Cardiovascular disease	5 (17.9%)	9 (12.3%)	0.52**
Gastrointestinal disease	6 (21.4%)	13 (17.8%)	0.78**
Lung function decline			
Decrease in FEV_1 (% pred)	2.74 (1.22)	−0.57 (0.89)	0.044*
No of rapid decliners†	12 (42.9%)	13 (17.8%)	0.009***

All subjects had a smoking history of at least 10 pack-years and had quit smoking at least 6 months before the study. Lung function was assessed as post-bronchodilator values of spirometry.
*Unpaired *t* test; **Fisher's exact test; ***χ^2 test.
†Rapid decline is defined as a mean annual decrease in FEV_1 ≥3.0% predicted.

The results of this study suggest that polymorphism of the *HO-1* promoter gene may be associated with the rate of decline in lung function in Japanese male ex-smokers. A larger study is needed to confirm this result. Although the reason for the discrepancy between the results of our study and that of He *et al*[4] is not clear, it might result from the difference in ethnic background of the participants. Since the susceptibility to COPD and/or decline in lung function could be influenced by a number of genetic and environmental factors, different polymorphisms in different ethnic groups may cause the same COPD phenotype. It is therefore important to confirm the associations of polymorphisms in each population. The L-allele carrier of the *HO-1* promoter gene in Japanese men is significantly associated with risks of developing lung adenocarcinoma,[5] pulmonary emphysema,[3] and less longevity.[2] Modification of *HO-1* gene expression may offer a new target for therapeutic intervention in lung disease in the Japanese population.

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