学 位 論 文 の 要 旨

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学 位 論 文 名　Functional Polymorphisms of the Cyclooxygenase-2 Gene and Risk for Chronic Obstructive Pulmonary Disease in Japanese Population

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論 文 内 容 の 要 旨

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by the progressive deterioration of pulmonary function and increasing airway obstruction. COPD is a multifactorial disease thought to arise due to a combination of environmental factors and accumulation of specific genetic alterations. Cyclooxygenase-2 (COX-2) is over-expressed and plays a biologically important role in inflammation of respiratory disease. However, there is insufficient evidence to define the relationship between COX-2 gene polymorphisms and COPD. The present study therefore examined the distribution of COX-2-765G>C and -1195G>A in COPD patients and healthy controls, to investigate a possible association between COX-2 polymorphisms and the risk of COPD in the Japanese population.

MATERIALS AND METHODS

One hundred and three patients with COPD and 129 healthy controls took part in this study. Patients were diagnosed based on clinical history, physical examination, and pulmonary functional tests, according to the GOLD criteria. The control subjects were sex- and age-matched, and had normal pulmonary function with no history of airway disease or abnormal findings on chest radiography. COX-2 genotypes were determined by polymerase chain reaction-restriction fragment-length polymorphism (PCR-RFLP) method. The x^2 test was used to evaluate the association between COX-2 genotype and COPD. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated.

RESULTS AND DISCUSSION

The distributions of the COX-2-765GG, GC, CC genotypes and G, C alleles were similar between COPD and control groups. The -765C allele was quite scarce, with no CC homozygote in either COPD or control subjects. The GC genotype was lower in COPD than control subjects (5.8% versus 10.9%), but the decreased risk was not significant (adjusted OR=0.509, 95%CI 0.181-1.376, P=0.223).

The COX-2-1195G>A polymorphism was more general, with similar distributions of -1195GG, GA genotypes and G, A alleles between the two groups, but a higher frequency of the -1195AA homozygote in COPD subjects than controls (44.6% versus 31.8%). The individuals who had the -1195AA genotype had an increased risk for COPD (adjusted OR=2.246, 95%CI 1.064-4.759, P=0.041).

The present study is the first one to assess the role of the COX-2 gene polymorphisms in COPD in the Japanese population. There was no significant difference in the genotype distribution and the allele frequency of COX-2-765G>C among the COPD and control groups. The -765GG genotype was more prevalent in the Japanese population, the frequency of -765GG genotype was 94.2% in COPD patients and 89.1% in controls. No -765CC homozygosity was

found in both groups. The distribution of the -765C allele was more in controls than COPD subjects (5.5% versus 2.9%), but the increase was not statistically significant (adjusted OR=0.478, 95%CI 0..126-1.988, *P*=0.445). The frequency of -765C allele had prodigious difference among various ethnic populations and diverse geographical area. There are many studies about the effect of COX-2-765CC genotype or -765C allele, but the conclusions are conflicting. These outcomes indicate that the COX-2-765G>C polymorphism may have a significantly different modulating effects on various disease phenotypes in different races and regions.

The current study was also the first that addressed the correlation between COPD and COX-2-1195G>A in the Japanese population. Individuals carrying -1195AA genotype had an increased risk for COPD. Polymorphism in COX-2-1195G>A are fairly common in humans. The distributions of -1195GG, GA and allele G, A were similar in the COPD and control groups, but the -1195AA genotype was higher in COPD subjects than controls (44.6% versus 31.8%), suggesting that the -1195AA was a risk genotype for COPD (P=0.041, adjusted OR:2.246, 95%CI:1.064-4.759). A possible mechanism for this effect is that the -1195A allele creates a c-Myb binding site to up-regulate the gene expression, thus the -1195A allele is a risk factor by increasing the promoter activity.

CONCLUSION

The current findings suggested that COPD was not associated with the COX-2-765G>C polymorphism, but not the COX-2-1195G>A polymorphism, the -1195AA genotype was a risk factor for COPD.