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Plasma Adiponectin Concentrations and Adiponectin Gene Polymorphisms Are Associated with Bronchial Asthma in the Chinese Li Population

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ABSTRACT

The purpose of this study was to determine the clinical significance of changes in the plasma adiponectin concentration in patients with bronchial asthma and to test the association between the single nucleotide polymorphisms (SNPs) rs2241766 and rs1501299 in the *ADIPOQ* gene and bronchial asthma in the Chinese Li population.

We selected 120 cases and 120 controls, and plasma adiponectin, interleukin (IL)-6, and tumor necrosis factor-alpha (TNF- α) levels were measured by enzyme-linked immunosorbent assay (ELISA). In addition, we genotyped two tag single nucleotide polymorphisms (tSNPs) and evaluated their association with bronchial asthma using the χ^2 test and genetic model analysis.

Compared to controls, patients with acute exacerbation of bronchial asthma showed significantly lower adiponectin and significantly higher IL-6 and TNF- α levels ($p < 0.01$). A positive association was found between the rs1501299 SNP and acute exacerbation (OR = 1.62; 95% CI = 1.08-2.43; $p = 0.019$).

The inverse correlation between the plasma adiponectin concentration and asthma exacerbation indicates that adiponectin may play a protective role in the pathogenesis of asthma. Meanwhile, our findings suggest that *ADIPOQ* polymorphisms influence the risk of developing bronchial asthma in Chinese Li population.

Keywords: Adiponectin; Asthma; Case-control studies

INTRODUCTION

Asthma is a serious public health problem in many

regions, including developing countries, where its incidence and mortality are increasing.¹ Over the last few decades, the prevalence of asthma has increased in many places around the world.² Asthma is a complex diseases involving complex interactions between multiple genes and environmental factors.^{3,4}

Adiponectin is a protein secreted from adipose

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Plasma Adiponectin Associated with Asthma

tissue in abundant amounts into the blood circulation. In mice, adiponectin has been shown to attenuate allergen-induced airway inflammation and hyper-responsiveness via induction of anti-inflammatory factors.⁵⁻⁷ Other studies have suggested that asthma is associated with intermediate biological and physiological phenotypes, including plasma adiponectin, interleukin (IL)-6, and tumor necrosis factor-alpha (TNF- α). Investigation shows, Chinese Li population asthma prevalence was 3.38%, significantly higher than the 1.50% prevalence of asthma in China.^{8,9} To investigate the potential role of *ADIPOQ* in the pathogenesis of asthma in the Chinese Li population, we determined the levels of plasma adiponectin, IL-6, and TNF- α in 120 bronchial asthma patients and 120 healthy controls of the Li nationality from the Hainan Province of China and determined whether there is an association between exacerbation of symptoms and the *ADIPOQ* single nucleotide polymorphisms (SNPs) rs2241766 and rs1501299.

MATERIALS AND METHODS

Study Participants

We recruited 120 Chinese Li (58 females, 62 males; median age = 53.5 \pm 6.9 years) diagnosed with bronchial asthma according to the guidelines developed by the Chinese Society of Respiratory Diseases Asthma Study Group in 1997. We used two different classifications for current asthma: 1) acute exacerbation was defined as episodes of recurrent wheezing, shortness of breath, chest tightness, or cough concurrent with a positive bronchodilator test; and 2) remission was defined as a diminishment of asthmatic symptoms and signs with or without treatment, restoration of lung function to the level before the onset of asthma attack, and retention of normal lung function for more than 2 weeks. The inclusion criteria for patient enrollment included no use of corticosteroids within the previous 1 week and no use of anti-asthma medications, such as a bronchodilator, within the 24 hours before blood sample collection.^{10,11} A total of 36 current asthma patients were classified as having acute asthma exacerbation and the remaining 84 patients were classified as being in remission. For control, 120 randomly selected healthy individuals (60 females, 60 males; median age 50.2 \pm 5.8 years) were taken as a control group, without previous or present medical history of respiratory disorders or symptoms (persistent

cough, sputum production, or dyspnea), seen by their practitioner for regular checkup, were recruited consecutively as controls. All participants were from Li populations of Hainan province.

Blood Sample Collection and Testing

The Human Research Committee of the People's Hospital of Hainan Province for Approval of Research Involving Human Subjects approved the use of human samples in this study. We also obtained signed informed consent from each study participant. Fasting blood samples were obtained from the elbow vein from all study participants. Blood samples were centrifuged at 2,500 r/min for 5 min at 4°C, and the resulting plasma was stored at -20°C. The plasma concentrations of total adiponectin, IL-6, and TNF- α were measured by enzyme-linked immunosorbent assay (ELISA) (adiponectin: Huian Biotech, Shenzheng, China; IL-6 and TNF- α : Sengxiong Biotech, Shanghai, China).

DNA Preparation and Genotyping

DNA was extracted following the phenol-chloroform protocol. The rs2241766 and rs1501299 variants of *ADIPOQ* were genotyped by polymerase chain reaction (PCR) amplification and restriction fragment length polymorphism (RFLP) analysis. The primers used for PCR amplification of *ADIPOQ* were designed using PrimerPremier 5.0 software, and the primers were synthesized and sequenced by Boya Biotech (Shanghai, China). The sequences of the PCR primers and restriction enzymes used were as follows: CTGAGATGGACGGAGTCCTTT (forward) and CCAAATCACTTCAGGTTGCTT (reverse), with *Sma*I (45 T>G) and *Mva*I 269I (276 G>T). We selected two tag SNPs (tSNPs) in *ADIPOQ*. All products of DNA cleavage were analyzed by electrophoresis on a 2% agarose gel and visualized using GIS Gel Imaging System software.

Statistical Analysis

Microsoft Excel and SPSS 16.0 statistical package (SPSS, Chicago, IL) were used to perform statistical analyses. All *p*-values in this study were two-sided, and a *p*-value \leq 0.05 was considered to indicate a significant difference. With the normality of data distribution for adiponectin, IL-6, and TNF- α . The frequency of each SNP in control subjects was validated by testing for departure from the Hardy-Weinberg equilibrium

(HWE) using an exact test. Differences in the tSNP genotype distribution between cases and controls were evaluated using the χ^2 test.¹² Unconditional logistic regression analysis was used to calculate the age-adjusted odds ratio (OR) and 95% confidence interval (CI).¹³ We evaluated the genetic association between genotype and bronchial asthma risk under different genetic models (co-dominant, dominant, recessive, over-dominant, and log-additive) using SNPstats, a website-based software available at <http://bioinfo.iconcologia.net>.¹⁴

RESULTS

Basic characteristics (e.g., gender, age, and pathology) of the cases and controls are listed in Table 1. No statistically significant differences were detected with respect to age, sex, and living environment

between the asthmatic and control groups, verifying the comparability of these two groups.

As shown in Table 2, adiponectin, IL-6, and TNF- α levels between cases and controls were compared by non-parametric Kruskal-Wallis test since adiponectin, IL-6, and TNF- α were not normally distributed in the outcome groups. Compared to the control group, patients with acute exacerbation of bronchial asthma showed significantly lower adiponectin and significantly higher IL-6 and TNF- α levels ($p < 0.01$). The level of adiponectin in patients in remission was significantly higher than that in patients with acute-stage asthma ($p < 0.01$) but was still lower than that in the controls ($p < 0.05$). The levels of both IL-6 and TNF- α in patients in remission were significantly lower than in patients with acute exacerbation ($p < 0.01$), but there were no differences in IL-6 and TNF- α levels between patients in remission and controls.

Table 1. Basic characteristics of cases and controls

| Variables | | Cases (n = 120) | | Controls (n = 120) | |
|-----------------|---------------------------|-----------------|------|--------------------|----|
| | | no. | % | no. | % |
| Sex | Male | 62 | 51.7 | 60 | 50 |
| | Female | 58 | 48.3 | 60 | 50 |
| Age (years) | Median age | 53.5 \pm 6.9 | | 50.2 \pm 5.8 | |
| Histologic type | acute asthma exacerbation | 36 | 30 | | |
| | remission stage | 84 | 70 | | |

Table 2. Comparison of plasma concentrations of adiponectin, IL-6, and TNF- α between healthy controls, patients with acute exacerbation of asthma, and patients in asthma remission

| Group | n | Adiponectin (ng/L) | IL-6 (ng/L) | TNF- α (ng/L) |
|--------------|-----|-------------------------------|------------------------------|------------------------------|
| Control | 120 | 24.6 \pm 8.9 | 26.3 \pm 11.5 | 29.5 \pm 12.6 |
| Exacerbation | 36 | 11.7 \pm 6.2 ^a | 56.4 \pm 19.3 ^a | 62.8 \pm 18.1 ^a |
| Remission | 84 | 19.3 \pm 7.5 ^{b,c} | 30.7 \pm 11.4 ^c | 35.6 \pm 14.6 ^c |

Concentration values are expressed as mean \pm SD.

^aCompared with Control group, $p < 0.01$; ^bCompared with Control group, $p < 0.05$;

^cCompared with Exacerbation group, $p < 0.01$

Table 3. Association statistics for SNPs in ADIPOQ

| SNPID | Base change | MAF (Case) | MAF (Control) | HWE p | OR | 95% CI | p -value |
|-----------|-------------|------------|---------------|---------|------|-----------|------------|
| rs2241766 | T>G | 0.30 | 0.30 | 0.08 | 1.02 | 0.69-1.51 | 0.921 |
| rs1501299 | G>T | 0.33 | 0.23 | 0.44 | 1.62 | 1.08-2.43 | 0.019* |

MAF: minor allele frequency; CI: confidence interval; OR: odds ratio.

* $P < 0.05$ indicates statistical significance.

Plasma Adiponectin Associated with Asthma

Table 4. Association between *ADIPOQ* tSNPs and the risk of bronchial asthma, based on logistic tests

| Model | Genotype | Control (n, %) | Case (n, %) | OR (95% CI) | p-value | AIC | BIC |
|---------------|----------|-------------------|----------------|------------------|---------|-------|-------|
| Co-dominant | G/G | 73 (60.8%) | 61 (50.8%) | 1.00 | 0.058 | 333 | 343.4 |
| | G/T | 39 (32.5%) | 40 (33.3%) | 1.23 (0.70-2.14) | | | |
| | T/T | 8 (6.7%) | 19 (15.8%) | 2.84 (1.16-6.94) | | | |
| Dominant | G/G | 73 (60.8%) | 61 (50.8%) | 1.00 | 0.12 | 334.3 | 341.2 |
| | G/T-T/T | 47 (39.2%) | 59 (49.2%) | 1.50 (0.90-2.51) | | | |
| Recessive | G/G-G/T | 112 (93.3%) | 101 (84.2%) | 1.00 | 0.023* | 331.5 | 338.5 |
| | T/T | 8 (6.7%) | 19 (15.8%) | 2.63 (1.10-6.28) | | | |
| Over-dominant | G/G-T/T | 81 (67.5%) | 80 (66.7%) | 1.00 | 0.89 | 336.7 | 343.7 |
| | G/T | 39 (32.5%) | 40 (33.3%) | 1.04 (0.61-1.78) | | | |
| Log-additive | - | - | - | 1.51 (1.04-2.20) | 0.03* | 332 | 339 |

MAF: minor allele frequency; OR: odd ratio; CI: confidence interval.

* $P < 0.05$ indicates statistical significance.

As shown in Table 3, two SNPs were genotyped in patients and controls. Both tSNPs were in HWE in the controls. We found that the rs1501299 tSNP in *ADIPOQ* was correlated with an increased risk of bronchial asthma at the 5% level (OR = 1.62; 95% CI, 1.08-2.43; $p=0.019$).

We assumed that the minor allele of each tSNP was a risk factor compared with the wild-type allele. The results of age- and gender-adjusted unconditional logistic regression analyses of different genetic models are presented in Table 4. In the recessive model of rs1501299 in *ADIPOQ*, genotype "TT" was associated with increased bronchial asthma risk (OR = 2.63; 95% CI, 1.10-6.28; $p=0.023$), whereas genotype "T" was associated with an increased risk in the log-additive model (OR = 1.51; 95% CI, 1.04-2.20; $p=0.03$).

DISCUSSION

In our current study, patients with acute exacerbation of bronchial asthma showed significantly lower adiponectin and significantly higher IL-6 and TNF- α levels ($p < 0.01$). A positive association was found between the rs1501299 SNP in *ADIPOQ* and acute exacerbation (OR = 1.62; 95% CI = 1.08-2.43; $p = 0.019$). The inverse correlation between the plasma adiponectin concentration and asthma exacerbation indicates that adiponectin may play a protective role in the pathogenesis of asthma. Meanwhile, our findings suggest that *ADIPOQ* polymorphisms influence the risk of developing bronchial asthma in Hainan Chinese Li population.

The adiponectin gene spanned 17 kb on chromosome 3q27, consisting of three exons and two introns.¹⁵ *ADIPOQ* encodes a protein consisting of 244 amino acids, a signal peptide, a collagen-like domain at its N-terminus, and a globular domain at its C-terminus.

The adiponectin protein is exclusively secreted from adipose tissue, mainly the white adipose tissue. Adiponectin modulates a number of metabolic processes, including glucose regulation and fatty acid metabolism, through its anti-diabetic, anti-inflammatory, anti-atherogenic, and anti-proliferative activities.^{16,17} Impaired adiponectin multimerization due to mutation is usually the causative factor for asthma. Asthma is a complex syndrome, broadly defined as inflammation of the airways associated with airway hyper-responsiveness (AHR) and mucus hypersecretion.¹⁸ Studies have demonstrated that adipose tissues express multiple adipocytokines that may influence airway inflammation and airway remodeling.^{19,20} In a murine model of acute asthma, treatment with adiponectin was shown to attenuate airway inflammation and AHR.⁶ Eosinophils, mast cells, T lymphocytes, neutrophils, airway epithelial cells, and various other types of cells participate in the pathogenesis of asthma. These cells release a number of cellular products, including histamine, arachidonic acid metabolites, and inflammatory cytokines such as IL-6, IL-8, and TNF- α , which induce development of airway obstruction, AHR, and inflammation. More specifically, it has been shown that adiponectin suppresses the production of TNF- α and IL-6 in

lipopolysaccharide-activated human and porcine macrophages.^{21,22} Adiponectin also suppresses production of the pro-inflammatory cytokine interferon-gamma (IFN- γ) by human macrophages.²³ These studies indicate that adiponectin may be an inhibitory regulator of the immune system and thus may suppress the inflammatory responses associated with asthma.²⁴

We determined whether there is an association between two SNPs in *ADIPOQ* (rs2241766 and rs1501299) and the risk of bronchial asthma in people of the Li nationality residing in Hainan Province, China. Our findings suggest a positive association between the rs1501299 SNP in *ADIPOQ* and acute exacerbations of asthma. Although the functions of most *ADIPOQ* SNPs remain unclear, Genome-wide association studies have identified several potentially functional *ADIPOQ* variants.²⁵⁻²⁷ It has been shown that two common SNPs, rs2241766 and rs1501299, may affect susceptibility to a variety of disorders, including obesity,²⁸⁻³⁰ type 2 diabetes mellitus,³¹⁻³³ cardiovascular disease,³⁴ colon cancer,³⁵ and chronic obstructive pulmonary disease.^{36,37}

In conclusion, we examined the hypotheses that polymorphisms in *ADIPOQ* may affect susceptibility to bronchial asthma and that low APN levels may increase asthmatic inflammation in the Chinese Li population. To the best of our knowledge, this is the first study that has investigated the association between the *ADIPOQ* SNPs rs2241766 and rs1501299 and bronchial asthma risk in persons of Li nationality residing in the Hainan Province of China. Our results are different from many previous studies finding. We confirmed *ADIPOQ* as an important asthma susceptibility gene in our study. Moreover, we illustrated that the gene plays a key role in asthma. However, our results need to be verified through repeat of our experiments in other populations, and the mechanisms underlying the role of adiponectin in asthma also require further investigation.

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Plasma Adiponectin Associated with Asthma

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