Association of FCGR2A/FCGR3A variant rs2099684 with Takayasu arteritis in the Han Chinese population

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ABSTRACT

Takayasu arteritis (TA) is a chronic large-vessel vasculitis of unclear pathogenesis. A recent genome-wide association study (GWAS) has revealed that the FCGR2A/FCGR3A, EEFSEC, RPS9/LILRB3, RIPPLY2 and MLX genes confer susceptibility to TA. We investigated the linkage between presumptive TA-related genes (FCGR2A/FCGR3A, EEFSEC, RPS9/LILRB3, RIPPLY2 and MLX) and TA in the Han Chinese population.

We performed a large case-control multi-center study of 412 Han Chinese TA patients and 597 ethnically matched healthy controls. Five single nucleotide polymorphisms (SNPs) were assessed and genotyped using Sequenom MassArray system (iPLEX assay, Sequenom, San Diego, CA, USA).

The frequency of the rs2099684 variant G allele in the FCGR2A/FCGR3A gene was significantly higher in the TA patients than in the controls (37.5\% compared with 25.4\%, OR =1.77, 95\% CI: 1.46–2.14, \textit{Pc} =1.5\times10^{-8}). Similar results were observed in genotype distribution analysis and logistic regression analyses conducted using three genetic models. The allele and genotype distributions for the other polymorphisms were not significantly associated with TA among the Han Chinese patients.

The SNP rs2099684 in FCGR2A/FCGR3A can be considered a genetic risk factor for TA in the Chinese Han population. These findings provide further insights into the etiopathogenesis of TA.

INTRODUCTION

Takayasu arteritis (TA) is a rare inflammatory disease typically characterized by non-specific inflammation of large arteries, especially the aorta and its major branches [1-3]. TA patients develop a wide range of symptoms, such as arterial stenosis, blood vessel wall thickening, dilation, progressive occlusion, and fibrosis, resulting in potentially life-threatening ischemia, aortic regurgitation, and pulselessness [1-3]. Other systemic symptoms may include myalgia, fatigue, arthralgia, fever, and weight loss. TA occurs all over the world and affects individuals of all ethnicities, but the highest prevalence rates have been described in Far East Asia, India, and Mexico, and this disease appears to be less common in European-derived individuals. Its reported incidence in North America is 2.6 cases per million per year [4]. However, its estimated incidence in Japan is approximately 40 cases per million [5]. Furthermore, the actual prevalence of this disease is unknown, as no large-scale epidemiological survey has been performed in China. TA is much more common in women, but the extent of this sex bias is dependent upon ethnicity and regional location [6, 7]. In addition, the average age of onset of this disease is between 20 and 40 years [6, 8].

The pathogenesis of TA has long been studied, but its etiology is largely unknown. The characteristic clinical features of TA, including the racial, ethnic, and geographic
differences, indicate a potential role of genetic factors in its pathogenesis. In fact, several lines of evidence suggest a genetic contribution to TA considering the ethnic differences in its prevalence, familial aggregation, cellular autoimmunity and genetic factors, especially the repeatedly confirmed genetic association with the human leukocyte antigen (HLA) region across multiple ethnicities [9-16]. HLA-B*52 is the gene most significantly associated with TA in the HLA region among TA patients. Saruhan-Direskeneli et al. conducted a genome-wide association study (GWAS) of TA, in which they assessed Turkish and North American TA patients by dense genotyping and imputation analysis [17]. This group confirmed that the most significant genetic association was in the HLA region. In addition, they identified a genetic association in the region that includes the genes encoding Fc-gamma receptor IIA (FCGR2A) and Fc-gamma receptor IIIA (FCGR3A), as well as two additional association effects of proteasome (prosome, macropain) assembly chaperone 1 (PSMG1), interleukin-12 (IL-12) and IL-23 (IL12B) that conferred a risk of TA but did not pass the threshold for genome-wide significance. Moreover, associations with the same genetic variants in IL12B have been described and confirmed in a Japanese cohort of TA patients [18]. Similarly, Renauer et al. carried out a GWAS on Turkish and North American TA patients and found that IL6 (rs2069837), RPS9/LILRB3, RIPPLY2 and MLX were associated with the disease [19].

It is widely accepted that racial and geographic differences and population heterogeneity are responsible for genetic predispositions to different diseases. The primary GWAS and candidate gene association studies were conducted on Turkish, North American and Japanese TA patients [17-19]. Thus, it is important to examine the relationships of the candidate genes with TA in the Han Chinese population. In the current study, we investigated gene polymorphisms in FCGR2A/FCGR3A, EEFSEC, RPS9/LILRB3, RIPPLY2 and MLX in 412 Han Chinese TA patients and 597 ethnically matched healthy individuals to evaluate the genetic factors associated with TA in this population.

RESULTS

The subjects’ characteristics

A total of 412 adult-onset TA patients (85.0% women; mean age, 31.6±10.8 years) and 597 ethnically matched healthy controls (85.3% women; mean age, 36.2±10.2 years) were included in this study. The characteristics of the patients and controls are summarized in Table 1. All SNPs were in HWE in the healthy controls (P_{HWE}>0.05). The genotype call rates of all SNPs were greater than 98%. The primary information for the five genotyped SNPs is shown in Table 2.

SNP analysis of the TA patients and controls from the Han population

The genotype and allele frequency distributions of the five SNPs are summarized in Table 3. The frequency of the rs2099684 variant G allele was significantly higher in the TA patients than in the controls (37.5% compared with 25.4%, OR = 1.77, 95% CI: 1.46-2.14, Pc = 1.5×10^{-8}, Table 3). Similarly, a significant difference in the genotypic distribution of rs2099684 was detected between the TA patients and controls (Pc = 4.9×10^{-7}, Table 3). However,
no significant association with TA was detected for any of the other SNPs among the patients (all, Pc > 0.05; Table 3).

The logistic regression analysis results are summarized in Table 3. Logistic regression analyses based on the genetic additive, dominant and recessive models yielded similar results, with stronger associations between rs2099684 and TA observed using the additive model (OR = 1.72, 95% CI: 1.43-2.07, Pc = 7.4×10^{-8}) and dominant model (OR = 1.87, 95% CI: 1.46-2.40, Pc = 5.0×10^{-6}). However, no significant differences were detected between the TA patients and healthy controls for the other SNPs using any of the three genetic models (all, Pc > 0.05, Table 4).

**DISCUSSION**

In this large-scale hospital-based case-control study, we investigated the associations of FCGR2A/
Previous studies have revealed that the prevalence of other inflammatory diseases in TA patients is high, suggesting that TA may be associated with immune system abnormalities activated by other inflammatory diseases, such as infection or inflammatory diseases of unknown origin [20]. FCGR2A/FCGR3A has been reported to be a susceptibility gene for other autoimmune diseases, such as systemic lupus erythematosus [21, 22], rheumatoid arthritis [23], multiple sclerosis [24], type 1 diabetes [23] and ulcerative colitis [25, 26]. In addition, a genetic association between the FCGR2A/FCGR3A polymorphism and giant cell arteritis (GCA) has been previously identified in a small cohort from Spain [27]. The findings of these studies indicate that these two large-vessel vasculitides might share common predisposing genes. Previously, GCA and TA have been considered distinct disorders based on their differing ages of onset and ethnic distributions. However, reports have claimed that these disorders have more similarities than differences, including similarities in several clinical features, angiographic findings, and the histopathological characteristics of arterial lesions [28, 29]. Thus, our results indicate that FCGR2A/FCGR3A might be a susceptibility gene for TA in patients from the Chinese Han population, suggesting that TA might share associated genetic loci with other autoimmune diseases.

The rs2099684 locus is located between the FCGR2A and FCGR3A gene regions on chromosome 1:161524048-161541759. The FCGR2A gene encodes one member of a family of immunoglobulin Fc receptors that are found on the surfaces of many immune response cells. The protein encoded by the FCGR2A gene is a cell surface receptor present on monocytes, macrophages, neutrophils, natural killer (NK) cells, and T- and B-lymphocytes, and it participates in diverse functions, such as phagocytosis of immune complexes and modulation of antibody production by B cells. In addition, it has important roles in the GPCR and phospholipase C pathways. The FCGR3A gene encodes a transmembrane receptor for the Fc portion of immunoglobulin G that is involved in the removal of antigen-antibody complexes from circulation, as well as other antibody-dependent responses. This receptor is expressed on activated monocytes/macrophages, NK cells, and a subset of T cells.

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| Gene          | SNPs                | Additive model | Dominant model | Recessive model |
|---------------|---------------------|---------------|---------------|----------------|
|               |                     | P<sub>c</sub> | OR (95%CI)    | P<sub>c</sub> | OR (95%CI)    | P<sub>c</sub> | OR (95%CI)    |
| FCGR2A/FCGR3A | rs2099684           | 7.4×10<sup>-6</sup> | 1.72(1.43-2.07) | 5.0×10<sup>-5</sup> | 1.87(1.46-2.40) | 4.9×10<sup>-5</sup> | 2.50(1.67-3.75) |
| EEFSEC        | rs10934853          | NS            | 0.89(0.75-1.07) | 0.21           | 0.76(0.58-0.99) | NS            | 1.03(0.75-1.42) |
| RPS9/LILRB3   | rs11666543          | 0.25          | 0.96(0.78-1.20) | 0.17           | 0.70(0.51-0.97) | NS            | 1.39(0.28-6.94) |
| RIPPLY2       | rs1570843           | 1.02(0.86-1.22) | NS            | 0.92(0.70-1.22) | NS            | 1.16(0.86-1.55) | NS            | 0.98(0.69-1.39) |
| MLX           | rs665268            | NS            | 0.90(0.75-1.08) | 0.59           | 0.82(0.63-1.05) | NS            | 0.98(0.69-1.39) |
studies. Therefore, the present investigation had sufficient statistical power to examine moderate and even marginal associations. Remarkably, our study revealed a significant positive association between the FCGR2A/FCGR3A (rs2099684) polymorphism and TA among the Chinese Han patients. Therefore, this SNP may play a potential role in the pathogenesis of TA. Nevertheless, we did not assess the role of the FCGR2A/FCGR3A (rs2099684) genetic variant in the development of TA in these patients.

In summary, the results of this study have demonstrated a strong relationship between the FCGR2A/FCGR3A (rs2099684) polymorphism and TA in patients from the Chinese Han population. Further investigations are needed to explore the associations of EEFSEC, RPS9/LILRB3, RIPPLY2 and MLX with TA in individuals of different ethnicities and from different regions.

MATERIALS AND METHODS

Subjects

This study was designed as a multi-center study that included 412 subjects with TA, diagnosed according to the American College of Rheumatology (ACR) criteria [30]. These patients were enrolled from two different sources; between February 2013 and July 2015, 230 patients were enrolled from the Peking Union Medical College Hospital. In addition, as this study was supported by the Research Special Fund for Public Welfare Industry of Health, 182 patients were recruited through the cooperation of 23 centers in China. Further, 597 healthy unrelated age- and sex-matched controls without any history of chronic disease were recruited from the Peking Union Medical College Hospital during physical examination. All patients and healthy individuals from the Chinese Han population of North China provided informed consent, and this study was approved by the Ethics Committee of the Peking Union Medical College Hospital.

Selection of single nucleotide polymorphisms (SNPs)

Based on the findings of previous GWASs of TA patients, five SNPs (rs2099684, rs10934853, rs11666543, rs1570843 and rs665268) in the FCGR2A/FCGR3A, EEFSEC, RPS9/LILRB3, RIPPLY2 and MLX genes were selected for analysis in this study (Table 2).

Genotyping

We collected 2-mL peripheral blood samples from the TA patients and healthy controls and extracted DNA from the peripheral white blood cells of each participant using kits purchased from Tiangen (Beijing, China), according to the manufacturer’s instructions. The genotyping of five SNPs was accomplished using a Sequenom MassArray system (Sequenom iPLEX assay, San Diego, CA, USA) according to the manufacturer’s guidelines.

The primers for polymerase chain reaction (PCR) and for locus-specific single-base extension were designed using MassArray Assay Design 4.0 (Sequenom). First, all of the DNA samples from the patients and controls were transferred to a 384-well plate. Second, after multiplex PCR amplification, the products were used for locus-specific single-base extension reactions. Third, the final products were subsequently desalted and transferred to a 384-element SpectroCHIP array (Sequenom). Fourth, allele detection was performed by matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS). Finally, the resultant mass spectrograms and genotype data were analyzed using MassArray Typer 4.0 software.

Statistical analysis

Statistical analysis was conducted using PLINK v1.07 software (Shaun Purcell, Boston, MA, USA) [31]. Hardy-Weinberg equilibrium (HWE) was assessed using the Chi-square ($X^2$) test for each SNP. Any SNPs that deviated from HWE ($P < 0.05$ in the control groups) were excluded from subsequent analysis. The genotype and allele distributions between the TA patients and healthy controls were evaluated using the $X^2$ test. $P$-values (corrected for multiple comparisons using the Bonferroni method) of less than 0.05 were considered statistically significant, and the odds ratios (ORs) and 95% confidence intervals (95% CIs) of associations were calculated. The genotype frequencies were further assessed using logistic regression models (additive, dominant, and recessive models).

ETHICAL STATEMENT

The study was approved by the Ethics Committee of the Peking Union Medical College Hospital.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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