Single Nucleotide Polymorphism rs10919543 in *FCGR2A/FCGR3A* Region Confers Susceptibility to Takayasu Arteritis in Chinese Population

Fang Qin[1], Hu Wang[2], Lei Song[1], Xi-Li Lu[1], Li-Rui Yang[1], Er-Peng Liang[1], Wei Wang[1], Yu-Bao Zou[1], Jin Bian[1], Hai-Ying Wu[1], Xian-Liang Zhou[1], Ru-Tai Hui[2], Hui-Min Zhang[1], Xiong-Jing Jiang[1]

[1]Hypertension Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, China

[2]State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing 100037, China

Abstract

Background: Takayasu arteritis (TA) is a rare inflammatory arteriopathy of unknown etiology. The aim of this study was to investigate the genetic susceptibility to TA in a Chinese population.

Methods: Four single nucleotide polymorphisms (SNPs) those locate in the *IL12B* region (rs56167332), the *MLX* region (rs665268), the *FCGR2A/FCGR3A* locus (rs10919543), and the *HLA-B/MICA* locus (rs12524487), associated with TA in different population, were genotyped in 123 Chinese TA patients and 147 healthy controls from January 2013 to August 2014. A Chi-square test was used to test for genotype/allele frequencies variants.

Results: Among the four SNPs, rs10919543 was found to be significantly associated with TA in the studied population. The GG genotype of rs10919543 at the *FCGR2A/FCGR3A* locus is a high risk factor (odds ratio [*OR*] = 6.532, 95% confidence interval [*CI*] = 2.402 − 17.763, *P* < 0.001) for TA. Among TA patients, the level of eosinophil granulocytes (Eos) in the peripheral blood was observed to be higher in the GG group of rs10919543 ($n = 23$, Eos = 0.11 [0.08, 0.17] $\times 10^9$/L) than the GA + AA group ($n = 100$, Eos = 0.08 [0.05, 0.13] $\times 10^9$/L, *P* = 0.028). No correlation between the genotypes of the other three SNPs and TA patients was observed.

Conclusions: Our findings revealed unique genetic pattern in Chinese TA patients that may be partly responsible for the higher risk of TA in this population. *FCGR2A/FCGR3A*-related immune disorder might contribute to the etiology of TA.

Key words: *FCGR2A*; *FCGR3A*; Single Nucleotide Polymorphisms; Takayasu Arteritis

INTRODUCTION

Takayasu arteritis (TA) is a rare systemic vasculitis characterized by nonspecific inflammation of the aorta and its major branches such as the carotid artery, the subclavian artery, the pulmonary artery, and the coronary artery.[1] The inflammation starts from the adventitia and progresses to the intima and leads to segmental stenosis, occlusion, dilatation, and/or aneurysm formation.[2] The disease is most prevalent in East Asia, India, Turkey, and Mexico. TA typically presents in young females, and the female-to-male ratio is dependent on ethnicity and geographical location.[3-5] Steroids and immunosuppressive drugs are the routine treatment for different types of TA, but many patients do not respond effectively to such therapeutics, and some may relapse during the gradual dose reduction of glucocorticosteroids.[6]

The etiology and pathogenesis of TA are largely unknown. Both environmental and genetic components have been shown to be involved with the onset of TA. The evidence for

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a genetic contribution to TA comes from ethnic differences in the prevalence of the disease, familial aggregation, and reports of affected twins. It has been reported that the major histocompatibility complex genes are associated with susceptibility to TA. The association with *HLA-B*52* is the strongest causative candidate to date in a Japanese population[7] and has been confirmed in other populations.[8,9] Other HLA alleles (including *HLA-B*39*, *HLA-DQB1/DRB1*, and *HLA-B*67:01*) have also been reported to be associated with this disease, although replication trials have shown contradictory results.[9-13] There are few commonly accepted causative genes, despite large numbers of studies attempting to clarify this. Recently, great efforts have been made to understand the genetic basis of TA through two large-scale genome-wide association studies (GWASs). These reports showed that single nucleotide polymorphisms (SNPs) nearby or within candidate genes in the Japanese population (*IL12B*, *MLX*, and *HLA-B*), and in population from Turkey and North America (*HLA-B/MICA*, *HLA-DQB1/HLA-DRB1*, *FCGR2A/FCGR3A*, and *IL12B*) are related to the susceptibility of TA.[14-15] This study was performed to confirm the correlation between the variants and TA in Chinese patients.

METHODS

Subjects

We calculated sample size based on previous studies of polymorphisms prevalence measuring differences between two proportions.[14] We took a two-tailed α error of 5% and β error of 20% using NCSS-PASS V11.0.7 for Windows package (Kaysville, UT, USA). The TA patients sample and healthy control size should be 142 cases for each group. However, TA is a rare disease, and the sample were limited, we increase the amount of control cohort. A total of 123 (111 females and 12 males, age of 34.3 ± 1.2 years, and range: 11–60) unrelated consecutive Chinese patients with TA were recruited from the Hypertension Center, Fuwai Hospital, Beijing, China from January 2013 to August 2014. Blood samples were collected after a 12 h overnight fast. A complete clinical history was obtained from all subjects and identified after data collection. One hundred and forty-seven age- and sex-matched healthy volunteers (120 females and 27 males, age of 34.6 ± 0.7 years, and range: 20–63) who provided written informed consent were collected as control samples. Each individual of the control group was interviewed by a physician so that any physiological disorder could be excluded, and data on their general medical history and information about their age, gender, and ethnicity were obtained. The study protocol was approved by the Ethics Committee of Fuwai Hospital, Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC).

Diagnostic and classification criteria

All patients fulfilled the American College of Rheumatology classification criteria for TA, fulfilling at least three of the following: age at disease onset <40 years old, claudication of extremities, decreased brachial artery pulse, blood pressure difference between both arms >10 mmHg,

bruit over subclavian arteries or aorta, and arteriogram abnormality.[16] Among the 123 patients, 74 cases underwent aortic and peripheral artery angiography, and others took computerized tomography angiography or magnetic resonance angiography at the time of diagnosis. They were classified into four types on the basis of Lupi-Herrera's *et al.* criteria: Type I, involvement of the aortic arch and its major branches; Type II, involvement of the thoracic and abdominal aorta; Type III, involvement of the whole aorta; and Type IV, involvement of the pulmonary artery.[17]

Disease activity and disease severity in patients with TA were defined according to the National Institute of Health (NIH) and Ishikawa's criteria, respectively. The group with disease active satisfied the NIH criteria if at least two of the following criteria were satisfied or they showed new onset or worsening of these features: systemic features (e.g., fever or musculoskeletal features) with no other cause identified; elevated erythrocyte sedimentation rate; and features of vascular ischemia or inflammation (e.g., claudication, diminished or absent pulses, bruit, vascular pain, asymmetric blood pressure in either the upper or lower limbs, and typical angiographic features).[18] Each patient was graded with mild-moderate or severe status at the time of diagnosis according to the Ishikawa classification, where mild-moderate status is defined as TA presence with none or one mild or moderate complication, and severe status is defined as TA with one severe complication or two or more complications. The following are the criteria for severity of each of the four complications. The estimation of the severity of Takayasu's retinopathy was made according to Uyama and Asayama's classification. Blood pressure values were graded with the severe form ≥200 mmHg brachial systolic and/or ≥110 mmHg diastolic, or ≥230 mmHg popliteal systolic and/or ≥110 mmHg diastolic. Severe aneurysm was defined as a diameter more than twice that of normal vessels. The severity of aortic regurgitation was estimated by angiography or echocardiography.[2]

Single nucleotide polymorphism selection and genotyping

GWASs recently found eight SNPs related to *IL12B*, *MLX*, *HLA-B*, *HLA-B/MICA*, *HLA-DQB1/HLA-DRB1*, and *FCGR2A/FCGR3A* genes are associated with TA. After excluding two SNPs which are considered as the proxy or to have synergetic effect of known genetic component in the Asia population[15,19] and two SNPs whose related genes (*HLA-DQB1* and *HLA-DRB1*) had been detected in the Chinese Han population,[20] four SNPs (rs56167332 in *IL12B* region, rs665268 in *MLX* region, rs10919543 within *FCGR2A/FCGR3A*, and rs12524487 within *HLA-B/MICA*), none of which have been examined in Chinese TA patients, were selected to test.

Peripheral blood (10 ml) was collected into tubes containing trisodium citrate and the plasma and cell buffy coat were kept at −70°C before use. Genomic DNA was extracted from leucocytes by the FlexiGene DNA Kit (Qiagen, Hilden, Germany). Genotyping was carried out by

polymerase chain reaction (PCR) and the Sanger sequencing method. The resultant PCR products were digested with NcoI (New England Biolabs, Beverly, Massachusetts, USA). Reproducibility of genotyping was confirmed by bidirectional sequencing in fifty randomly selected samples, and the reproducibility was 100%. All experiments were carried out at State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, CAMS and PUMC, China.

Statistical analysis

The distribution of quantitative variables was tested for normality by a one-sample Kolmogorov–Smirnov test. The normal distribution continuous variables are expressed as mean ± standard deviation (SD) and the nonnormal distribution ones are expressed as the median (P_{25}, P_{27}). The mean levels of variables were compared using a one-way analysis of variance (ANOVA) or nonparametric test, and the Chi-square test was used to analyze the association of the four polymorphisms with susceptibility to TA and the Hardy–Weinberg equilibrium. The association was expressed as an odds ratio (OR). The pooled ORs were performed for a recessive model (GG vs. GA + AA), dominant model (GG + GA vs. AA), and additive model (GG vs. GA vs. AA) for the rs10919543. For other polymorphisms, we evaluated the same effects. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) for Windows statistical package.

RESULTS

Participant characteristics

The clinical characteristics of 123 patients with TA and 147 healthy controls are shown in Table 1. The mean age of patients with TA was 33.6 ± 13.1 years and 90% were female. The mean onset age of TA was 24.9 ± 10.0 years. There were 39 patients (32%) in the active phase of the disease at enrollment. In total, 41% of the patients suffered Type III TA, while 20%, 21%, and 18% were classified as

Table 1: Demographic characteristics of patients with TA and healthy controls

Items	TA patients (n = 123)	Control (n = 147)
Age (years), mean ± SD	33.6 ± 13.1	34.6 ± 0.7
Gender (female), n (%)	111 (90)	120 (82)
Age of onset (years), mean ± SD	24.9 ± 10.0	–
Clinical classification, n (%)		–
Type I	25 (20)	–
Type II	26 (21)	–
Type III	50 (41)	–
Type IV	22 (18)	–
Severity classification (severe TA), n (%)	61 (50)	–
Disease activity (active TA), n (%)	39 (32)	–
Percentage of hypertension, n (%)	83 (68)	0
Use of glucocorticoids, n (%)	100 (81)	0

TA: Takayasu arteritis; –: Not applicable.

Types I, II, and IV TA, respectively. Sixty-one (50%) of 123 patients had one severe or more complications. Totally, 100 patients (81%) received prednisone therapy [Table 1].

Association of single nucleotide polymorphisms with Takayasu arteritis

Significant differences were found in the rs10919543 allele ($P = 0.001$) and genotype frequencies ($P = 0.001$) in TA patients compared with controls [Table 2] ($\chi^2 = 11.39$ and 17.39 separately). The recessive model (GG vs. GA + AA) of rs10919543 allele demonstrated remarkably increased risk of TA (OR = 6.532, 95% confidence interval [CI] =2.402 − 17.763, $P < 0.001$). Hence, did in the dominant (GG + GA vs. AA) (OR = 1.870, 95% CI = 1.272 − 2.749, $P = 0.001$) and additive model (GG vs. GA vs. AA) (OR = 1.628, 95% CI = 1.001 − 2.645, $P = 0.032$) [Table 3]. Among the TA patients group, the level of eosinophil granulocytes (Eos) was found to be higher in the SNP rs10919543 genotype GG group ($n = 23$, Eos = 0.11 [0.08, 0.17] ×10^9/L) than in the GA + AA group ($n = 100$, Eos = 0.08 [0.05, 0.13] ×10^9/L, $P = 0.028$), no other correlation of rs10919543 genotype and clinical characteristics was observed [Table 4]. This association is independent of steroid use. There were no statistical differences in the distribution of the rs56167332, rs665268, and rs12524487 allele and genotype frequencies between TA patients and controls.

No evidence of departure from the Hardy–Weinberg equilibrium in the TA and control group for any genotyped polymorphisms was observed.

DISCUSSION

Many studies have demonstrated that HLA alleles contribute to susceptibility for TA. However, few evidences for associations between non-HLA genes and TA have been reported. Two large-scale genetic analyses have been performed recently, revealing some new candidate genes.[14-15] Three non-HLA genes (FCGR2A/FCGR3A, IL12B, and MLX) and one HLA gene (HLA-B/MICA) related SNPs, which have been previously reported to be associated with TA in Japanese, Turkish, and American populations, were replicated in our Chinese TA cohort, the SNP rs10919543 in FCGR2A/FCGR3A gene was found to have a solid effect on vulnerability to TA with an OR of 6.532. However, the role of SNPs associated with gene IL12B, MLX, and HLA-B/MICA were failed to show a significant difference of allele and genotype frequencies in patients relative to controls in our study which was not consistent with the GWAS results.[14-15]

The infiltration of the artery wall with inflammatory cells in TA strongly suggests that cell-mediated immunological mechanisms play an important role in the pathogenesis of this disease. However, few studies have confirmed the importance of humoral immunity in TA pathogenesis. Eichhorn et al. have shown that antiendothelial cell antibodies (AECAs) are frequently present in patients with TA,[21] and an animal model provided further evidence that

Table 2: Genotype and allele frequencies in patients with TA and healthy controls

Gene	SNP ID	TA patients (*n* = 123) (*n*/frequency)			Control (*n* = 147) (*n*/frequency)			Risk allele	MAF		P		
									Case	Control	Recessive	Dominant	Additive
IL12B	rs56167332	CC	CA	AA	CC	CA	AA	A	0.341	0.262	0.271	0.052	0.075
		54	54	15	82	53	12						
		0.439	0.439	0.122	0.558	0.361	0.082						
MLX	rs665268	AA	AG	GG	AA	AG	GG	G	0.427	0.387	0.641	0.320	0.549
		40	61	22	56	67	23						
		0.325	0.496	0.179	0.384	0.459	0.158						
FCGR2A/FCGR3A	rs10919543	AA	AG	GG	AA	AG	GG	G	0.398	0.264	<0.001	0.032	0.001
		48	52	23	74	67	5						
		0.390	0.423	0.187	0.507	0.459	0.034						
HLA-B/MICA	rs12524487	CC	CT	TT	CC	CT	TT	T	0.278	0.187	0.161	0.168	0.081
		72	41	10	98	43	6						
		0.585	0.333	0.081	0.667	0.293	0.041						

MAF: Minor allele frequency; TA: Takayasu arteritis; SNP: Single nucleotide polymorphisms.

Table 3: Association of four SNPs with TA compared with the controls in the population

Genotypes	Recessive model for rs10919543	Additive model for rs10919543	Dominant model for rs10919543	Dominant model for rs56167332	Dominant model for rs665268	Dominant model for rs12524487
	GG versus GA + AA	GG versus GA versus AA	GG + GA versus AA	AA + AC versus CC	GG + GA versus AA	TT + TC versus CC
Crude *OR*s (95% *CI*)	6.532 (2.402–17.763)	1.870 (1.272–2.749)	1.628 (1.001–2.645)	0.620 (0.383–1.005)	0.775 (0.468–1.282)	0.706 (0.430–1.159)
P	<0.001	0.001	0.032	0.052	0.320	0.168

*OR*s: Odds ratios; *CI*: Confidence interval; SNPs: Single nucleotide polymorphisms; TA: Takayasu arteritis.

Table 4: Associations between clinical manifestations of TA and rs10919543 genotypes in a recessive model

Items	GG (*n* = 23)	GA + AA (*n* = 100)	Statistics	*P*
Age (years)	33 ± 13	36 ± 14	−1.194*	0.232
Gender (female), *n* (%)	20 (87)	91 (91)	0.347†	0.556
Age of onset (years)	24 ± 1	25 ± 10	−0.565*	0.572
TA duration (months)	86.0 (37.5, 240.0)	42.7 (10.8, 147.6)	−1.888*	0.059
ESR (mm/h)	13 (6, 27)	9 (5, 19)	−0.832*	0.406
CRP (mg/L)	29.8 (17.3, 97.8)	34.5 (17.4, 84.4)	−0.079*	0.995
Eos (×10⁹/L)	0.11 (0.08, 0.17)	0.08 (0.05, 0.13)	−2.194*	0.028
Clinical classification, *n* (%)			2.370†	0.678
Type I	3 (13)	22 (22)		
Type II	4 (17)	22 (22)		
Type III	11 (48)	39 (39)		
Type IV	5 (22)	17 (17)		
Severity classification (severe), *n* (%)	11 (48)	50 (50)	0.035†	0.851
Disease activity (active TA), *n* (%)	9 (39)	30 (30)	0.720†	0.396
Percentage of hypertension, *n* (%)	16 (70)	67 (67)	0.056†	0.813
Use of glucocorticoids, *n* (%)	18 (78)	82 (82)	0.172†	0.739
TB infection history, *n* (%)	1 (4)	7 (7)	0.095†	0.758

Values were showed as mean ± SD, *n* (%), or median (P$_{25}$, P$_{75}$). ESR: Erythrocyte sedimentation rate; CRP: C-reaction protein; Eos: Eosinophil granulocyte; TB: Tuberculosis; TA: Takayasu arteritis; SD: Standard deviation; *: *Z* values; †: χ^2 values.

AECA could be pathogenic.[22] The involvement of antiaorta antibodies has also been reported in patients with TA,[23] but the effect of this is still controversial. Studies have also demonstrated that TA patients often have antiphospholipid antibodies.[24] Genes that encode molecules critical to the immune response may be responsible for the immune regulation disorder.

In our results, people with SNP rs10919543 genotype of GG have a 6.532 times risk on vulnerability to TA. The global minor allele frequency (MAF) of rs10919543 is 0.2802 from 1000 genome phase 1 genotype data from 1094 worldwide individuals released in the May 2011 dataset. The MAF of rs10919543 for Han Chinese in Beijing is 0.3447. This is different with the frequency of our results which is

examined in patients and controls from multiple provinces in China. The *FCGR2A* and *FCGR3A* genes are members of the Ig gene superfamily that encode immunoglobulin Fc receptors found on the surface of many immune response cells. Variations of this gene family affect receptor functions such as phagocytosis and clearing of immune complexes. It is critical for the immune system to recognize foreign antigens by receptors on the surface of cells of macrophages, neutrophils, and eosinophils. *FCGR* gene polymorphisms have been reported to be associated with several human autoimmune diseases. For example, rs1801274 of *FCGR2A* is a nonsynonymous SNP that has been reported to be associated with lupus erythematosus, glomerulonephritis, and ulcerative colitis.[25-28] In addition, Morgan performed a case–control study for giant cell arteritis (GCA) in the Spanish population that indicated that *FCGR2A* might play an important role in GCA etiology.[29] Interestingly, according to the definitions of Chapel Hill consensus,[30] TA and GCA may represent a spectrum of the same disease as both of them occur mostly in women and have similar histopathological findings. Our study demonstrates an *FCGR2A*/*FCGR3A*-related SNP associated closely to TA, providing new evidence that the GCA might share common genetic susceptibility loci with TA, implying that there might exist similar etiology mechanism for the two kinds of large arteritis. Our study provided more evidences for etiology of humoral immunity for TA patients. Among population with higher risk SNP genotype, factors that influence whom will develop TA remains to be illuminated.

The association of TA with HLA genes such as *HLA-B*52*, *HLA-B*39*, *HLA-DQB1/DRB1*, and *HLA-B*67:01* have been reported by a lot of researchers including GWASs. Most of the results were definitive, but some were still controversial.[7-13] In this Chinese TA population, we replicate SNPs in 123 TA patients, which is a relatively large cohort for such rare disease. One *HLA-B/MICA*-related SNP was not proved significant. Meantime, GWAS recently revealed that the SNPs of the *IL12B* gene which modulates the level of cytokines and the SNP of the *MLX* gene which regulates gene expression by forming heterodimers with mad protein were significantly associated with clinical manifestations of TA.[31] These results were in accordance with the findings of Terao *et al*.[9] However, SNPs related to the *IL12B* and the *MLX* gene showed negative findings in our study. The lack of association might be explained by the different racial origins or the number limitation of the study cohort.

We observed the level of Eos was higher in the rs10919543 genotype GG group than in the GA + AA group in the 123 TA patients. Eos is one kind of immunocyte. The activation of Eos can release an array of cytotoxic granule cationic proteins that are capable of inducing tissue damage and dysfunction.[32] We speculated that the genotype distribution difference of Eos might imply the potential immune effect during the disease course of arteritis. The detailed mechanism needs further study.

In conclusion, we confirmed that the rs10919543 allele in the *FCGR2A*/*FCGR3A* gene is involved in susceptibility to

TA, and the GG genotype is a high-risk factor in Chinese TA population. *FCGR2A*/*FCGR3A*-related immune disorder may be responsible for the vulnerability of TA.

Conflicts of interest

There are no conflicts of interest.

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