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Polymorphisms of the TIM-1 gene are associated with rheumatoid arthritis in the Chinese Hui minority ethnic population

J.R. Xu[1,2], Y. Yang[1,2], X.M. Liu[1,2] , J.Y. Sun[1,2] and Y.J. Wang[1,2]

[1]Key Laboratory of the Ministry of Education for Conservation and Utilization of Special Biological Resources in Western China, Yinchuan, China
[2]College of Life Science, Ningxia University, Yinchuan, Ningxia, China

Corresponding author: Y.J. Wang
E-mail: wyj@nxu.edu.cn / yujiongw@gmail.com

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ABSTRACT. The T-cell immunoglobulin and mucin domain 1 (TIM-1) is known to be associated with susceptibility to rheumatoid arthritis (RA). We investigated the association of four single-nucleotide polymorphisms (SNPs) in the promoter region of the TIM-1 gene with susceptibility to RA in a Chinese Hui ethnic minority group. Using RFLP or sequence specific primer-PCR, 118 RA patients and 118 non-arthritis control individuals were analyzed for the -1637A>G, -1454G>A, -416G>C, and -232A>G SNPs in the TIM-1 gene. The polymorphisms -232A>G and -1637A>G in the promoter region of TIM-1 were found to be associated with susceptibility to the RA gene in the Hui population, while -416G>C and -1454G>A SNPs were not. Of these, the polymorphism of -232A>G is inconsistent with that found in a Korean population, suggesting that genetic variations of the TIM-1 gene contribute to RA susceptibility in different ways among different populations. Based on haplotype analysis, individuals with haplotypes AGCA (χ^2 = 22.0, P < 0.01, OR (95%CI) >1), AGCG (χ^2 = 18.16, P < 0.01, OR (95%CI) >1) and AGGA

(χ^2 = 5.58, P < 0.05, OR (95%CI) >1) are at risk to develop RA in the Chinese Hui population; those with the GAGA (χ^2 = 7.44, P < 0.01, OR (95%CI) <1) haplotype may have a decreased likelihood of RA. GGCA and GGCG are more common in both RA and non-RA subjects. We conclude that -1637A>G and -232A>G polymorphisms of TIM-1 are associated with susceptibility to RA in the Chinese Hui population.

Key words: TIM-1; Polymorphism; Haplotype; Rheumatoid arthritis; Chinese Hui population

INTRODUCTION

T-cell immunoglobulin domain and mucin domain (TIM) proteins have been reported to be expressed on T cells and are involved in the regulation of T helper (Th) cells immune responses and allergic diseases such as asthma and rheumatoid arthritis (RA) (Chae et al., 2003, 2004a, 2005; Gao et al., 2005; Mou et al., 2010). The TIM gene family consists of eight genes on mouse chromosome 11B1.1, and three genes lie on the human chromosome 5q33.2. All three human genes encode for cell surface glycoproteins with common structural motifs. These motifs include: signal peptides, Ig domains, mucin domains, transmembrane regions, and intracellular tails with phosphorylation sites, referred to as TIM1 (OMIM 606518), TIM3 (OMIM 606652), and T-cell immunoglobulin and mucin domain containing protein 4 (TIMD4; OMIM 610096) (Kuchroo et al., 2003).

The human TIM1 gene encodes a type 1 transmembrane glycoprotein composed of an immunoglobulin variable region (IgV)-like domain, a mucin-like domain, a transmembrane region, and a cytoplasmic tail, initially cloned as kidney injury molecule 1 (KIM1) and hepatitis A virus cellular receptor 1 (HAVCR1) (Feigelstock et al., 1998; Ichimura et al., 1998, 2008). TIM-1 is selectively expressed on activated $CD4^+$ T cells and sustained preferentially on Th2 cells. Thus, it has been considered to be a membrane protein associated with the development of Th2-biased immune responses (Abbas et al., 1996; Hofstra et al., 1998; McIntire et al., 2001; Kuchroo et al., 2003).

The Th cells are sub-divided into Th1 or Th2 cells based on the cytokines produced and distinct functions performed (Abbas et al., 1996). Both Th1 and Th2 cells play critical roles in the regulation of cellular and humoral immune responses. The balance of Th1 and Th2 cells is crucial in the immune response to allergens and pathogens. For instance, Th1 cell-induced autoimmune diseases may be inhibited by predominant induction of Th2 cells. Th2 cell induction inhibits the hypersensitivity and organ-specific autoimmune diseases such as RA, but may mediate asthma and other allergic diseases (Schulze-Koops and Kalden, 2001). Furthermore, predominant induction of Th1 cells can inhibit Th2 cell-induced allergic diseases, such as asthma (Kuchroo et al., 2003; Meiler et al., 2006).

RA, one of the most common chronic autoimmune disorders, is probably caused by the interaction of multiple disease susceptibility genes and environmental factors (Gregersen, 2001, 2003). This disease has been characterized as inflammation of synovial tissues and formation of rheumatoid panni. These panni lead to the erosion of adjacent cartilage and bone resulting in joint destruction. Selective expression on Th2 cells may suggest that TIM-1 is a candidate susceptibility gene associated with Th cell-mediated allergic and autoimmune diseases. Recent population studies have demonstrated that genetic variations in TIM-1 were

associated with susceptibility to both allergic diseases and autoimmune diseases (Chae et al., 2003, 2004a,b, 2005; Gao et al., 2005; Wu et al., 2009a,b). Furthermore, previous polymorphism studies performed on the TIM-1 promoter region in a Korean population have identified a promoter polymorphism, -1637A>G, to be associated with susceptibility to RA in a Korean population (Chae et al., 2005). This study suggests that genes in the TIM-1 promoter region contribute to the genetic portion of RA, and the polymorphisms of this gene may serve as important candidate markers of RA.

The Chinese Hui ethnic minority descended from Arabic and Persian merchants who came to China during the 7th century. With a population of over 12 million, the majority of the group live in the Ningxia Hui Autonomous Region. To retain religious purity and group identity, the Hui have always segregated themselves socially from other people, in enclaves. Hui marriage practices tend toward endogamy in all respects, especially in the rural part of Ningxia Hui Autonomous Region. The Hui population is culturally and religiously conservative.

Previous studies performed by Chae et al. (2004a, 2005) have revealed direct correlations between specific TIM-1 allelic variants in the promoter region and exon 4 leading to increased susceptibility to RA in a Korean population. While recent studies demonstrated that the RA susceptibility of genetic variants of 4q27, 6q23, CCL21, TRAF1/C5, CD40, and PTPN22 in Caucasian populations they did not contribute significantly to RA in Koreans; this implies various genetic risk factors for RA to exist among different populations (Lee et al., 2009). The aim of this study was to investigate whether the above single-nucleotide polymorphisms (SNPs) in the promoter region of TIM-1 gene identified in Korean population contribute to the susceptibility of RA in the Chinese Hui ethnicity. We assessed the associations between TIM-1 polymorphisms in RA patients and the non-arthritis controls from the Chinese Hui population.

MATERIAL AND METHODS

Subjects

Blood samples were collected from 118 RA patients and 118 non-arthritis control individuals of the Chinese Hui population living in the Ningxia Hui Autonomous Region of China. The Revised ARA Criteria for the Classification of Rheumatoid Arthritis by the American Rheumatism Association was used to diagnose a patient with RA (Clegg and Ward, 1987; Arnett et al., 1988). The non-RA controls were recruited from the general Hui population and had undergone comprehensive medical screening at the Affiliated Hospital of Ningxia Medical University. All subjects were included in this study based on two criteria: of purely Hui descents for at least three generations and individual ancestors who have lived in the Ningxia region for at least three generations. There was no genetic relationship among these individuals. All the samples were collected with informed consent.

Single nucleotide polymorphism analysis

The genomic DNA of leukocytes from peripheral blood was extracted using sodium dodecyl sulfate lysis and proteinase K digestion, followed by a standard phenol-chloroform extraction method (Chae et al., 2005). Sequence specific primer-polymerase chain reaction (SSP-PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP) were performed on four SNPs in the promoter region of TIM-1 gene. PCR was performed in a 25-µL total re-

action volume using 200 ng genomic DNA and using a PCR amplification kit. The DNA was amplified for 35 cycles at 94°C for 30 s, 58-65°C for 45 s (Table 1), and 72°C for 45 s, with a final extension at 72°C for 5 min using the BioRad MyCycler Thermal Cycler (BioRad Laboratories, Hercules, CA, USA). Genotyping for -232A>G and -1637A>G SNPs in the TIM-1 gene was performed by SSP-PCR as previously reported with the primer sets listed in Table 1 (Chae et al., 2003). The PCR-RFLP analysis was employed for genotyping the -1454G>A and -416G>C polymorphic sites of the TIM-1 gene as described previously; the primer sets used for PCR and restriction endonucleases used for digestion are listed in Table 1 and Table 2 (Chae et al., 2005). For SSP-PCR analysis (-232A>G and -1637A>G SNPs), the PCR products were resolved on 1.5% agarose gel in the presence of ethidium bromide. For PCR-RFLP analysis (-1454G>A or -416G>C polymorphic sites), the PCR products were purified by using a PCR purification kit, followed by digestion with restriction endonuclease of *Taq*I or *Msp*I (Table 2). The digested PCR products were run on 2% agarose gel containing ethidium bromide. The PCR product and digested product sizes are listed in Table 2. The PCR reaction kit, PCR purification kit and restriction endonucleases were products of Takara Biologicals (Japan).

Table 1. Primer sets used for amplifying the four polymorphisms in the promoter region of the TIM-1 gene.

Polymorphism position	Primer sequence	Annealing (°C)
TIM-1 (-232A>G)	F1: 5'-TCAGGGGCTGTTTCTGTGGA-3'	59
	F2: 5'-TCAGGGGCTGTTTCTGTGGG-3'	59
	R: 5'-CATCTTGCCTTGTTCATTTAGC-3'	59
TIM-1 (-1637A>G)	F1: 5'-CTTCCAGGTTCAAGCAATTCTTCTA-3'	60
	F2: 5'-CTTCCAGGTTCAAGCAATTCTTCTG-3'	60
	R: 5'-AATCGGGCTGTTGACTTCTGCT-3'	60
TIM-1 (-416G>C)	F: 5'-GCATGTTGTACAGGAGCATGA-3'	65
	R: 5'-GCAGACAGGCTGGTTGGTACC-3'	65
TIM-1 (-1454G>A)	F: 5'-CAGGTTGGTCTCAAACTCCTT-3'	58
	R: 5'-TTCCAAGGAGGCAGTGGTGG-3'	58

Table 2. Determination of the TIM-1 genotypes using SSP-PCR or PCR-RFLP assay.

SNP	Size of PCR product (bp)	Primer set	Restricted enzyme	Fragments of RFLP (bp)	Genotype
SSP-PCR					
-232A>G	533	F1/R	N/A	N/A	GG
		F2/R	N/A	N/A	AA
		F1, F2/R	N/A	N/A	AG
-1637A>G		F1/R	N/A	N/A	GG
		F2/R	N/A	N/A	AA
		F1, F2/R	N/A	N/A	AG
PCR-RFLP					
-416G>C	879	F/R	*Taq*I	879, 488, 391	GC
				488, 391	GG
				879	CC
-1454G>A	511	F/R	*Msp*I	511, 395, 116	GA
				395, 116	GG
				511	AA

N/A = not available.

Statistical analysis

Genotype and allele carrier frequency were defined as the percentage of individuals carrying the genotype and allele of the total number of individuals, respectively. The chi-square

test and the Fisher exact test of SPSS 13.0 for Windows (SPSS Inc., Chicago, ILL, USA) were used to test for deviation from the Hardy-Weinberg equilibrium, and compare to the frequency of discrete variables between RA patients and control individuals. For RA patient-control haplotype analyses, the SHEsis Online haplotype analysis software (http://analysis.bio-x.cn/myAnalysis.php) was applied. A P value of <0.05 was considered to be statistically significant.

RESULTS

The four SNPs in the promoter region of TIM-1 gene have been previously investigated for their associations with the susceptibility to asthma and RA in a Korean and Chinese Han populations (Chae et al., 2003, 2004b, 2005; Mou et al., 2010). To determine if these SNPs were also associated with susceptibility to RA in the Chinese Hui ethnicity, we analyzed the polymorphisms of the TIM-1 gene at the sites of -1637A>G, -1454G>A, -416G>C, and -232A>G in 118 RA patients and 118 non-arthritic controls from the Hui population. The polymorphic analysis of -1454G>A or -416G>C sites was performed by the PCR-RFLP assay and -232A>G and -1637A>G site analysis was conducted by the SSP-PCR method.

Following the *Taq*I and *Msp*I digestion of PCR products at the -416G>C and -1454G>A polymorphic sites, respectively, all three genotypes were determined for each SNP, the genotype AA at -1454G>A site was very infrequent in this study (Figure 1, Table 2 and data not shown). Statistical analysis demonstrated no significant difference in the genotype and allele frequencies of -416G>C, and -1454G>A polymorphisms between RA patients and controls from the Hui ethnicity ($P > 0.05$, Table 3). This result was consistent with the previous report (Chae et al., 2005). However, the genotype and allele frequencies at -1637A>G polymorphic site were significantly different between the RA patients and controls ($P < 0.01$; Table 3). The G allele of the -1637A>G SNP was significantly less common in RA patients than in controls ($P < 0.01$), while the A allele of the -1637A>G SNP was significantly more common in RA patients than in controls ($P < 0.01$). The genotype frequencies at -232A>G polymorphic site was significantly different in control subjects compared to RA patients ($P < 0.01$; Table 3); while no significant difference was observed in the allele frequencies of -232A>G site between the two populations ($P > 0.05$; Table 3) due to a high frequency of heterozygous (AG) detected in the control individuals. These results suggest that both -232A>G and -1637A>G polymorphisms of the TIM-1 gene may be strongly associated with RA susceptibility in the Hui ethnicity. This finding is different from that previously observed in the Korean population, which stated that no significant difference in the genotype and allele frequencies of -232A>G was found between the RA patients and non-arthritic controls (Chae et al., 2004b).

We next analyzed the haplotypes of the TIM-1 gene in RA patients and controls from the Chinese Hui population using the SHEsis Online haplotype analysis software. Fifteen of the sixteen possible haplotypes were detected in the samples for this study. The AACG haplotype was not detected in either the RA patients or controls and haplotypes GAGG, AAGA and AAGG were not detected in the control subjects in this study (Table 4). Furthermore, statistically significant differences were observed in the distribution of haplotype frequency for haplotypes AGCA and AGCG between the RA patients and controls ($\chi^2 = 22.00$ and 18.16, respectively, $P < 0.01$, OR (95%CI) >1) (Table 4); Statistically significant differences were also found in the haplotype frequency distribution of AGGA between the two groups ($\chi^2 = 5.58$, $P < 0.05$, OR (95%CI) >1) (Table 4). The haplotypes AGCA, AGCG and AGGA apparently were at risk haplotypes associated with RA in this study (underlined in Table 4, $P < 0.01$).

However, statistically significant differences in the controls and patients were also observed in the distribution of the GAGA haplotype ($\chi^2 = 7.44$, $P < 0.01$, OR (95%CI) <1). The GAGA haplotype was associated with decreased likelihood of RA (in bold and italic letters in Table 4), and GGCA and GGCG are more common in the non-RA subjects as well. These findings suggested that -1637A>G and -232A>G polymorphisms of the TIM-1 gene may be two of the most important genetic factors associated with susceptibility to RA in the Hui ethnicity.

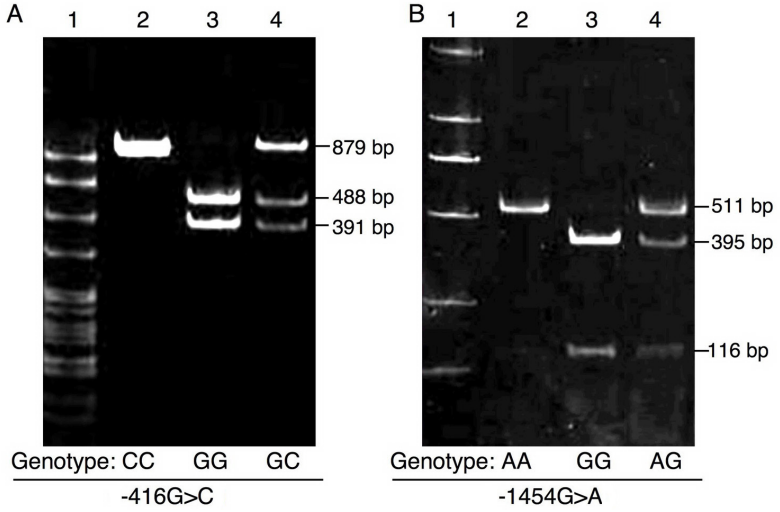

Figure 1. Genotype analyzed by PCR-RFLP method for the -416G>C and -1454G>A polymorphisms of the TIM-1 gene. The PCR amplified products were digested with: **A.** *Taq*I (for -416G>C, left panel) or **B.** *Msp*I (for -1454G>A, right panel) before they were resolved on an agarose gel. *Lane 1* = DNA molecular ladders; *lanes 2*, *3* and *4* = the corresponding genotypes labeled at the bottom of each picture.

Table 3. Genotype and allele analyses of the polymorphisms of the TIM-1 gene in rheumatoid arthritis (RA) patients and non-arthritis controls in the Chinese Hui population.

Position	Genotype/allele	Control [N (%)]	RA [N (%)]	χ^2	P
-1637A>G	AG	33 (28.0)	65 (55.0)	37.41	<0.01
	AA	20 (17.0)	37 (31.3)		
	GG	65 (55.0)	16 (13.7)		
	A	74 (31.3)	140 (59.3)	30.69	<0.01
	G	164 (68.7)	96 (40.7)		
-1454G>A	AG	26 (22.0)	26 (22.2)	0.55	>0.05
	AA	2 (1.7)	4 (3.7)		
	GG	90 (76.3)	86 (74.8)		
	A	31 (13.1)	35 (14.8)	0.29	>0.05
	G	205 (86.9)	201 (85.2)		
-416G>C	GC	67 (56.7)	75 (63.6)	1.97	>0.05
	GG	10 (8.5)	13 (11.0)		
	CC	41 (34.8)	30 (25.4)		
	G	87 (36.9)	100 (42.4)	1.32	>0.05
	C	149 (63.1)	136 (57.6)		
-232A>G	AG	67 (56.8)	39 (33.1)	13.52	<0.01
	AA	32 (27.1)	45 (38.1)		
	GG	19 (14.4)	34 (28.8)		
	A	133 (56.4)	128 (54.2)	0.17	>0.05
	G	103 (43.6)	108 (45.8)		

Table 4. The haplotype frequencies of the four TIM-1 SNPs in rheumatoid arthritis (RA) patients and non-arthritis controls in the Chinese Hui Population.

Haplotypes				Frequency (%) [a]		χ^2	P [b]	OR [95%CI] [c]
-1637	-1454	-416	-232	RA	Control			
A	A	C	A	0.020	0.024	-	-	-
G	A	C	A	0.015	0.030	0.77	>0.05	0.519 [0.18~2.30]
G	A	C	G	0.013	0.033	1.43	>0.05	0.399 [0.08~1.89]
A	G	C	A	0.156	0.020	22.00	<0.01	9.611 [3.13~29.52]
G	G	C	A	0.134	0.302	13.16	<0.01	0.374 [0.22~0.64]
A	G	C	G	0.207	0.060	18.16	<0.01	4.361 [2.12~8.96]
G	G	C	G	0.035	0.159	14.49	<0.01	0.199 [0.08~0.49]
G	***A***	***G***	***A***	0.001	0.052	7.44	<0.01	0.023 [0.002~0.26]
G	A	G	G	0.018	0.000	-	-	-
A	G	G	A	0.093	0.035	5.58	<0.05	2.990 [1.16~7.71]
G	G	G	A	0.075	0.109	0.96	>0.05	0.694 [0.33~1.45]
A	G	G	G	0.039	0.000	6.46	<0.05	166.9 [10.6~2637.8]
G	G	G	G	0.134	0.176	0.86	>0.05	0.760 [0.42~1.36]
A	A	G	A	0.027	0.000	-	-	-
A	A	G	G	0.032	0.000	6.15	<0.05	
A	A	C	G	0	0	-	-	-

Underlined letters = haplotypes at risk associated with RA; bold and italic letters = haplotypes associated with decreased likelihood of RA. [a]Values were constructed by EM algorithm with genotyped SNPs. [b]Values were analyzed by the permutation test. [c]Values were analyzed by the χ^2 test from R x C contingency table.

DISCUSSION

RA is a complex autoimmune disease involving risk factors from both genetics and the environment. A large body of studies show evidence that the genetic factors are key risk factors of RA susceptibility in various ethnicities. The list of risk loci for RA has been continually expanding (Chae et al., 2004b, 2005; Lee et al., 2009; Nordang et al., 2009; Munoz-Valle et al., 2010; Raychaudhuri, 2010). Previously identified novel RA-associated loci were early steps to understanding the genetic contribution to RA, and other studies and our study presented in this report further convinced us of the association of a specific variant with RA, suggesting that either the variant or a highly correlated nearby gene of the TIM-1 gene may play a critical role in the pathogenesis of RA. Thus, pathways involved in this gene may be targeted effectively for therapeutic purpose in the early stage of RA.

A candidate SNP approach has been an effective means to discover RA-associated risk alleles. Previous studies using such approaches have demonstrated that the TIM-1 gene may be associated with susceptibility to allergic diseases and autoimmune diseases including RA in Korean (Chae et al., 2003, 2004a,b, 2005), Chinese Han population (Liu et al., 2007; Wu et al., 2009a,b; Mou et al., 2010) and Japanese populations (Noguchi et al., 2003). In the present study, we analyzed four SNPs in the human TIM-1 gene of the Chinese Hui population. In agreement with that found in a Korean population the -1637A>G polymorphism in the promoter region of the TIM-1 gene was strongly associated with RA susceptibility (Chae et al., 2005). The results presented in this report also demonstrate tight association of -1637A>G polymorphisms with RA susceptibility in the Hui population. Therefore, the -1637A>G site may be an important risk genetic variant for RA in many ethnicities. Different from the observed lack of association of the -232A>G polymorphism with RA in Korean population (Chae et al., 2005), we report a strong association of this polymorphism in the Chinese Hui population. This suggests that genetic variations of the TIM-1 gene contribute to RA suscepti-

bility among different populations. This is consistent with the findings that genetic variants of TIM-1 lead to asthma susceptibility in different populations (Chae et al., 2003; Noguchi et al., 2003; Gao et al., 2005; Li et al., 2006; Liu et al., 2007).

The Hui population is one of the 56 nationalities in China with a population of over 12 million. The majority of this population currently resides in the Ningxia Autonomous Region. To our knowledge, this is the first report of TIM-1 polymorphisms in the Hui ethnicity. Our results show the significant association of the -232A>G and -1637A>G SNPs in the TIM-1 gene promoter with RA susceptibility, and individuals carrying an A allele of -1637A>G site in the TIM-1 gene may be at higher risk for RA in this population. In contrast, individuals with heterzygotes (AG) of -232A>G site in the TIM-1 gene have a decreased likelihood of RA (Table 3). Haplotype analysis based on the four SNPs in the promoter region of the TIM-1 gene indicated that the haplotypes AGCA, AGCG and AGGA were risk haplotypes associated with RA in the Hui ethnic population, and the haplotype GAGA was associated with a decreased likelihood of RA.

In conclusion, we determined that polymorphisms of -232A>G and -1637A>G in the promoter region of the TIM-1 gene, but not -416G>C and -1454G>A are potential genetic variants for RA in the Chinese Hui population; furthermore, the -1637A>G polymorphism is associated with RA susceptibility. Individuals with haplotypes AGCA, AGCG and AGGA are at risk to RA in this ethnicity, and those with haplotypes GAGA may have a decreased likelihood of RA.

Conflict of interest

The authors declare that there are no conflicts of interest.

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