ORIGINAL ARTICLE

Association Between *TIM-1* Gene Polymorphisms and Allergic Rhinitis in a Han Chinese Population

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Abstract

Background: TIM-1, a member of the T cell immunoglobulin and mucin (TIM) domain family, is involved in T-cell differentiation and has been implicated in allergic diseases. An association between *TIM-1* and allergic rhinitis, however, has not been established.
Objective: To investigate whether *TIM-1* gene polymorphisms were associated with allergic rhinitis in a Han Chinese population.
Methods: Two *TIM-1* promoter single nucleotide polymorphisms (SNPs), -416G>C and -1454G>A, were examined in 185 allergic rhinitis patients of Han Chinese ethnicity using polymerase chain reaction (PCR) and restriction fragment length polymorphism. Additionally, exon 4 insertion/deletion polymorphisms in the *TIM-1* gene were analyzed by PCR, polyacrylamide gel electrophoresis, and silver staining. The relationship between gene polymorphisms and serum specific IgE levels in this Han Chinese population was also evaluated.
Results: We found that the -416G>C and -1454G>A SNPs were associated with allergic rhinitis susceptibility in this Han Chinese population. No statistically significant differences in the distribution of genotype or allele frequencies of 5383_5397ins/del and 5509_5511delCAA in exon 4 were observed. The -416G>C and -1454G>A SNPs were associated with the level of serum IgE specific to house dust mites in patients with allergic rhinitis.
Conclusions: These results suggest that *TIM-1* gene polymorphisms (-416G>C and -1454G>A) are associated with allergic rhinitis susceptibility in a Han Chinese population.

Key words: T-cell immunoglobulin and mucin domain molecule-1. Gene polymorphisms. Allergic Rhinitis. Chinese Population. Han.

Resumen

Antecedentes: El gen *TIM-1*, un miembro de la familia portadora del dominio mucina e inmunoglobulina de linfocito T (TIM), participa en la diferenciación de linfocitos T, y se ha relacionado con enfermedades alérgicas. No obstante, no se ha establecido ninguna asociación entre *TIM-1* y la rinitis alérgica.
Objetivo: Investigar si los polimorfismos del gen *TIM-1* estaban asociados a la rinitis alérgica en una población china de la etnia Han.
Métodos: En 185 pacientes con rinitis alérgica de la etnia china Han, se estudiaron dos polimorfismos de nucleótido simple (SNP) en la región promotora de *TIM-1* (-416G>C y -1454G>A) mediante reacción en cadena de la polimerasa (PCR) y polimorfismo de longitud de fragmentos de restricción. Además, se analizaron polimorfismos de inserción/deleción del exón 4 en el gen TIM-1 mediante PCR, electroforesis en gel de poliacrilamida y tinción de plata. Igualmente, se evaluó la relación entre los polimorfismos genéticos y los niveles séricos de IgE específica en esta población china de la etnia Han.
Resultados: Se halló que los SNP -416G>C y -1454G>A presentaban relación con la susceptibilidad a la rinitis alérgica en esta población china de la etnia Han. No se observaron diferencias estadísticamente significativas en la distribución del genotipo o las frecuencias alélicas de 5383_5397ins/del y 5509_5511delCAA en el exón 4. Los SNP -416G>C y -1454G>A se asociaron al nivel sérico de IgE específica a ácaros del polvo doméstico en pacientes con rinitis alérgica.
Conclusiones: Estos resultados indican que los polimorfismos del gen *TIM-1* (-416G>C y -1454G>A) presentan relación con la susceptibilidad a la rinitis alérgica en una población china de la etnia Han.

Palabras clave: Molécula 1 con un dominio mucina e inmunoglobulina de linfocito T. Polimorfismos genéticos. Rinitis alérgica. Población china. Etnia Han.

Introduction

During the past few decades, the prevalence of allergic diseases such as allergic rhinitis and asthma has shown a remarkable increase worldwide [1]. Allergic rhinitis is characterized by hyperresponsiveness, overproduction of type 2 helper (T_H2) cytokines, and selective eosinophil accumulation in the nasal mucosa [2]. According to the hygiene hypothesis, the increased incidence of allergic rhinitis results from a complex interplay between genetic and environmental factors, with the latter playing a critical role [3,4]. Although allergic rhinitis has been studied extensively, the pathogenesis of the allergic response is still not well understood [5].

Several recent genetic studies have identified numerous loci in the human genome that are believed to harbor genes associated with atopy [5-7]. Chromosome 5q, in particular, has received much attention as this region harbors several candidate genes, including the T_H2 cytokines interleukin (IL) 4 and IL-13 [5-7]. The T-cell immunoglobulin and mucin domain (TIM) gene family, located at 5q33, regulates T-cell proliferation and T_H1/T_H2 differentiation. This family is comprised of *TIM-1*, *TIM-3*, and *TIM-4* in humans, and encodes T-cell membrane proteins with immunoglobulin (Ig) and mucin-like domains [6,7]. In mice, *TIM-1* polymorphisms have been associated with the regulation of T_H2 cytokine production and airway hyperresponsiveness [8], both hallmarks of allergic rhinitis and asthma.

Polymorphisms of the human *TIM-1* gene appear to be associated with the allergic response as well. Such polymorphisms, for example, have been linked to total serum levels and may explain the association between childhood infections and the development of allergy [9]. Furthermore, the frequency of the homozygous deletion variant (157delMTTTVP) in the fourth exon of the *TIM-1* gene has been reported to be higher in patients with asthma compared to controls in an African-American population, suggesting that genetic variants of *TIM-1* contribute to asthma susceptibility [10]. Similar results have been found in a Korean population [11]. In addition, Chae et al [12] have suggested a direct correlation between certain *TIM-1* allelic variants in exon 4 of the gene and susceptibility to rheumatoid arthritis in a Korean population. Noguchi et al [13], for their part, have reported that insertion/deletion polymorphisms in *TIM-1* are not associated with atopic asthma in the Japanese population. While an association between *TIM-1* polymorphisms and atopic dermatitis has been reported in a Chinese population [14], whether or not *TIM-1* polymorphisms affect susceptibility to allergic rhinitis in the Chinese population has not been investigated.

In previous studies, we have shown *TIM-1* expression to be upregulated in murine models of allergic rhinitis and asthma and to be associated with T_H2 differentiation [15,16]. To shed further light on whether or not genetic alterations of *TIM-1* are involved in the development of allergic rhinitis, we genotyped single-nucleotide polymorphisms (SNPs) and exon 4 insertion/deletion polymorphisms in a Han Chinese population with allergic rhinitis. Our findings regarding the association between this disease and *TIM-1* polymorphisms will contribute to a better understanding of the pathogenesis of the allergic respiratory response.

Patients and Methods

Patients

We recruited 185 allergic rhinitis patients sensitized to house dust mites (HDMs) for the study. The diagnosis of allergic rhinitis was based on case history, patient complaints, nasal/endoscopic inspection, allergen skin prick tests, and serum IgE assays (UniCAP system, Pharmacia, Uppsala, Sweden). All the patients were assessed using the standard allergic rhinitis criteria in the Allergic Rhinitis and its Impact on Asthma (ARIA) document (including a typical history of sneezing, rhinorrhea, nasal obstruction, swollen turbinate, positive specific IgE (>0.35kU/L), and a positive skin prick test to HDM [5]. Allergic rhinitis severity was also classified using the ARIA guidelines. We recruited 178 age-matched healthy volunteers as controls. The nonatopic status of controls was evaluated by allergen skin prick tests and specific IgE levels(<0.35kU/L). None of the study participants had received medication in the 4 weeks prior to their recruitment. They were all of Han ethnicity, nonsmokers, and had not had an upper respiratory tract infection in the 4 weeks preceding the study. The demographic characteristics of the patients and controls are listed in Table 1. The study was approved by the local ethics committee, and informed consent was obtained from all participants.

For gene detection, 10 to 20 mL of peripheral blood was collected from each individual and kept in EDTA-treated tubes to prevent coagulation. DNA was subsequently extracted from isolated leukocytes using a standard protocol for genotyping.

Genotyping

Two SNPs in the *TIM-1* promoter region, -1454G>A and -416G>C, were genotyped using polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis as described previously [14]. PCR amplification was performed in a GeneAmp PCR System 2400 thermal cycler

Table 1. Demographic Characteristics of Allergic Rhinitis (AR) Patients and Controls

	AR Patients (n=185)	Healthy Controls (n=178)
Mean (SD) age, y	28.9 (13.5)	31.4 (17.2)
Sex, male/female	101/84	97/81
Mean (SD) time since onset, y	4.5 (1.9)	NA
Mean (SD) total IgE lefel, kU/L	155 (58.4)	35.7 (15.3)
Mean (SD) HDM-specific IgE level, kU/L	57.5 (21.9)	<0.35

Abbreviations: HDM, house dust mite; IgE, immunoglobulin E; NA, not applicable.

(PerkinElmer, Wellesley, Massachusetts, USA). The primer pairs, 5'-AAT CAT AGC CTC CAA CTG C-3' and 5'-CCC ACA TGC GTT AAA TCG-3' CTG GGC and 5'-AAT GAC CAA GAT TGA C-3' and 5'-CTC ACT CTA GAC TGT CCT TCT-3', respectively, were used to amplify the -1454G>A and -416G>C polymorphisms. PCR was performed in a total volume of 25 µL solution containing 50 ng of genomic DNA, 200 µM of each dNTP (mixture of dATP, dTTP, dCTP, dGTP), 0.2 µM of each primer, 1.5 mM of MgCL2, 10 mM of Tris hydrochloride (pH 8.3), and 1 U of Taq DNA polymerase (Promega, Madison, Wisconsin, USA). Cycling conditions included an initial denaturation step at 94°C for 5 minutes followed by 35 cycles at 94°C for 40 seconds, 55°C for 40 seconds, 72°C for 60 seconds, and a final extension at 72°C for 10 minutes. PCR products were digested with locus-specific restriction enzymes according to the manufacturer's instructions (Msp I for -1454G>A and TaqI for -416G>C) (NEB, Ipswich, Massachusetts, USA). Digestion products were separated on a 1.5% agarose gel and visualized by ethidium bromide staining.

The exon 4 insertion/deletion polymorphism in the *TIM-1* gene was genotyped by PCR, carried out in a similar manner to that described above. The PCR primers used were 5'-GTT TGA CTT ATG CTC ACT CTC-3' and 5'-CCT CAC TCT AGA CTG TCC TTC-3'. Amplification was performed at an initial denaturation step at 94°C for 5 minutes followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 60°C for 30 seconds, and an extension at 72°C for 60 seconds. A final extension was carried out at 72°C for 10 minutes. Blank amplification reactions were run to check for the presence of contamination. PCR products were separated on a 6% denatured polyacrylamide gel and visualized by means of silver staining. To genotype the exon 4 polymorphism, PCR products containing the SNP were digested with TaqI restriction enzyme for 2 hours at 65°C according to the manufacturer's instructions. Subsequently, the digestion products were electrophoresed on a 2% agarose gel containing ethidium bromide and visualized by means of ultraviolet transillumination. In both assays, PCR products from individuals with ascertained genotypes were used as standards. The genotyping results were confirmed by direct sequencing of a subgroup of samples with the forward primers used in the PCR. Sequencing analysis was performed by BigDye Terminator cycle sequencing using an ABI 3100 PRISM Automated DNA sequencer (Applied Biosystems, Foster City, California, USA) according to the manufacturer's instructions. For quality control, strict measures in all laboratory procedures were applied. To minimize the risk of contamination during DNA extraction and PCR, the controls and patients were not genotyped in separate batches and analysis was blindly performed with respect to case-control status.

Statistical Analysis

Allele carrier frequency was defined as the percentage of individuals carrying the allele of the total number of individuals. The χ^2 and Fisher exact tests were used to test for deviations from the Hardy-Weinberg equilibrium, and to compare the frequency of discrete variables between patients with allergic rhinitis and healthy controls. SPSS 13.0 for Windows (SPSS

Table 2. Genotype and Allele Frequencies of 2 *TIM-1* Gene Promoter SNPs in Patients With Allergic Rhinitis (AR) and Healthy Controls

Position	Genotype/ Allele	Healthy Controls No. (%)	AR Patients No. (%)	Odds Ratio (95% CI)	*P*
-416	GG	109 (61.2)	92 (49.7)	1.00	
	GC	51 (28.6)	54 (29.2)	1.254 (0.897-1.754)	.105
	CC	18 (10.2)	39 (21.1)	2.567 (1.151-3.012)	.001
	G	269 (75.6)	238 (64.4)	1.00	
	C	87 (24.4)	132 (35.6)	1.715 (0.995-2.441)	.028
-1454	GG	119 (66.9)	93 (50.3)	1.00	
	GA	48 (27.0)	47 (25.4)	1.253 (0.875-1.608)	.089
	AA	11 (6.1)	45 (24.3)	5.234 (2.339-6.571)	.001
	G	286 (80.3)	233 (62.9)	1.00	
	A	70 (19.7)	137 (37.1)	2.402 (1.798-3.005)	.002

Abbreviations: CI, confidence interval; SNP, single nucleotide polymorphism.

Table 3. Genotype and Allele Frequencies of *TIM-1* Gene Exon 4 Polymorphisms in Patients With Allergic Rhinitis (AR) and Healthy Controls

Position[a]	Genotype/ Allele	Healthy Controls No. (%)	AR Patients No. (%)	Odds Ratio (95% CI)	P^{b}
53_5397[d] el	Genotype 1[c]	11 (6.2)	8 (4.3)	1.00	
	Genotype 2[d]	49 (27.5)	60 (32.4)	1.683 (0.876-1.992)	.094
	Genotype 3[e]	118 (66.3)	114 (62.3)	1.328 (0.584-1.102)	.225
	Allele 1[f]	71 (19.9)	76 (20.5)	1.00	
	Allele 2[g]	285 (80.1)	294 (79.5)	0.963 (0.685-1.275)	.401
5509_5511[d] elCAA	Genotype 1[c]	107 (60.1)	131 (70.8)	1.00	
	Genotype 2[d]	51 (28.7)	39 (21.1)	0.625 (0.305-0.981)	.297
	Genotype 3[e]	20 (11.2)	15 (8.1)	0.613 (0.412-1.011)	.204
	Allele 1[f]	265 (74.4)	301 (81.4)	1.00	
	Allele 2[g]	91 (25.6)	69 (18.6)	0.667 (0.379-1.082)	.179

Abbreviation: CI, confidence interval.
[a]Calculated from the translation start site.
[b]Determined by $\chi 2$ test from a 2×2 and 2×3 contingency table.
[c]Denotes homozygous control sequence.
[d]Denotes heterozygous sequences of control and variation (5383_5397 del or 5509_5511delCAA).
[e]Denotes homozygous variation sequence.
[f]Denotes control sequences.
[g]Denotes variation sequences.

Inc., Chicago, Illinois, USA) was used to compare allele and genotype frequencies, calculate odds ratios with their 95% confidence intervals, perform multivariate logistic regression analysis, and analyze significance. Comparisons of the levels of total serum IgE and specific IgE to HDM for the different genotypes were performed using the analysis of variance test. A *P* value of <.05 was considered statistically significant. For stringently significant analysis, Bonferroni correction was applied, with statistical significance set at *P*<.0125.

Results

The allele frequencies of 2 SNPs (-416G>C, -1454G>A) in *TIM-1* were determined in 185 patients with allergic rhinitis and 178 healthy controls of Han Chinese ethnicity. The distributions of the 2 SNPs were in agreement with the Hardy-Weinberg equilibrium (*P*>.05) in both groups and the frequencies were between 6.1% and 66.9% (Table 2). The genotype and allele frequencies of each SNP were compared between patients and controls. The G allele of the–416G>C SNP was significantly less common in patients than in controls after Bonferroni correction (*P*=.001), while the A allele of the -1454G>A SNP was significantly more common in patients than in controls, also after Bonferroni correction (*P*=.001). Multivariate logistic regression analysis adjusted for age and sex also confirmed this association. These results suggest that the –416G>C and -1454G>A SNPs in the *TIM-1* promoter region are significantly associated with allergic rhinitis in patients of Han Chinese ethnicity.

Additionally, 5383_5397ins/del and 5509_5511delCAA in exon 4 of the *TIM-1* gene were examined. The genotyping of exon 4 revealed the presence of 3 alleles and 5 genotypes for 5383_5397ins/del, while 2 alleles and 3 genotypes were identified for 5509_5511delCAA. The genotype and allele frequencies of each polymorphism are shown in Table 3. No significant difference was observed in genotype or allele frequencies for the polymorphisms between the 2 groups after Bonferroni correction (*P*>.05). Deviations from the Hardy-Weinberg equilibrium were examined for all 3 polymorphisms, with no significant deviations found in either the patients or controls (*P*>.05).

To further determine the association between *TIM-1* gene polymorphisms and allergic rhinitis, we analyzed the association between the 2 SNPs in the *TIM-1* promoter with total serum IgE and HDM-specific IgE levels. As illustrated in Table 4, we found these polymorphisms to be significantly associated with HDM-specific IgE levels (P<.05) but not with total serum IgE levels (*P*>.05) in patients.

Table 4. Association Between SNP Genotypes and Levels of HDM-Specific Immunoglobulin (Ig) E in Patients With Allergic Rhinitis (AR)

	Genotype	Mean (SD) Specific IgE, kU/L	*P*
-416 G>C	GG	56.9 (23.4)	.035
	GC	22.8 (12.5)	
	CC	29.3 (15.7)	
-1454 G>A	GG	47.5 (23.1)	.029
	GA	20.5 (8.3)	
	AA	16.2 (8.9)	

Abbreviations: HDM, house dust mite; SNP, single nucleotide polymorphism.

Discussion

In the present study, we investigated *TIM-1* gene promoter polymorphisms (-416G>C and -1454G>A) in a Han Chinese population with allergic rhinitis. To our knowledge, this is the first report of such polymorphisms in allergic rhinitis patients. Certain *TIM-1* polymorphisms have been previously demonstrated in different populations with asthma and atopic dermatitis, establishing a possible genetic linkage for the *TIM-1* gene to atopic diseases in humans [11,14,17-19]. Consistent with these findings, our study identified 2 SNPs in the *TIM-1* promoter (-416G>C, 1454G>A), but no insertions/deletions in exon 4 of the *TIM-1* gene. These SNPs, thus, are likely to play an important role in susceptibility to allergic rhinitis in our population.

The central role of T cells in the pathogenesis of allergic disease is well established [20]. Through the production of IL-4, IL-5, and IL-13, allergen-specific T_H2 cells direct IgE synthesis, eosinophil growth and differentiation, and induction of airway hyperresponsiveness. Recently, it was proposed that the basis for allergic disease was an imbalanced T_H cell response to certain allergens, manifested as a predominance of T_H2 cytokines over T_H1 cytokines [21]. While the role of T_H2 cells in the pathogenesis of allergic disease is clear, the mechanisms underlying the predominance of these cells are less well characterized. A number of reports suggest that *TIM-1* mRNA is expressed by T_H2 but not T_H1 cells in humans and mice, and that *TIM-1* is upregulated by $CD4^+$ T cells after stimulation [22,23]. Moreover, our previous studies indicate that *TIM-1* may participate in the modulation of transcription factors such as T-bet and GATA-3 [15,16], which are essential for the differentiation of T_H1/T_H2 subsets. Therefore, the ability of *TIM-1* to modulate T_H2 cell differentiation in vitro has important implications for the prevention of allergic disease.

In an attempt to explain the genetic tendency of atopic diseases, numerous candidate genes residing in a syntenic chromosomal region (5q33.2) linked to susceptibility to allergy and autoimmune diseases were screened for genetic polymorphisms [24]. *TIM-1* attracted much attention when the *TIM-1* protein was found to be the receptor for hepatitis A virus [25], and epidemiologic data revealed that atopic diseases were less common among children who had had hepatitis A [26]. More recently, polymorphisms of the *TIM-1* gene were found to be linked to susceptibility to asthma in a Korean and a Caucasian-American population [9,10]. Chae et al [9] reported that in a Korean population, 5383_5397ins/del was associated with atopic dermatitis but not with asthma, whereas 5509_5511delCAA was associated with both atopic dermatitis and asthma. In another study, Gao et al [10] reported that in an African-American population, the frequency of a homozygous deletion variant (157delMTTTVP) in the fourth exon of the *TIM-1* gene was higher in patients with asthma than in controls, suggesting that the genetic variants of *TIM-1* contribute to asthma susceptibility. However, we failed to detect a significant association between polymorphisms in exon 4 and allergic rhinitis in the Han Chinese population, which is in agreement with previous reports on Chinese and Japanese patients with asthma [13,14].

The results of the present study show the association between 2 SNPs in the *TIM-1* gene promoter (-416G>C, 1454G>A) and allergic rhinitis in patients of Han Chinese ethnicity. This confirms findings from a report on Chinese patients with asthma [14], suggesting homogeneity among Chinese patients of Han ancestry. In that study, Liu et al utilized luciferase reporter assays to further examine the potential function of the *TIM-1* promoter polymorphism, and found that the transcriptional activity of the *TIM-1* gene was affected. Interestingly, in previous reports, based on a murine model of allergic rhinitis, we found that *TIM-1* expression was enhanced in atopic conditions [15,16]. This observation led us to suspect that *TIM-1* gene polymorphisms may possess some clinical relevance. To further investigate this possibility, we analyzed the association between 2 SNPs in the *TIM-1* promoter, -416G>C, 1454G>A, and HDM-specific IgE levels. As anticipated, we found the association to be significant in patients with allergic rhinitis and decided to investigate whether there was an association between *TIM-1* gene polymorphisms and allergic rhinitis in a Han Chinese population. The limitations of this preliminary study include our failure to perform a specific haplotype and diplotype analysis and possible distortion of findings due to false positive report probability, insufficient statistical power, and α error. For this reason, further studies are needed to further confirm the association between the 2 SNPs genotyped and allergic rhinitis.

In conclusion, our results demonstrate that the genetic variation in the *TIM-1* gene promoter (-416G>C and 1454G>A) is a possible risk factor for allergic rhinitis in individuals of Han Chinese ethnicity, and suggest that targeting *TIM-1* may represent a novel and potentially useful means for atopic disease prevention.

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