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Association of Thymic Stromal Lymphopoietin Receptor (*TSLPR*) Polymorphisms with the Susceptibility of Rheumatoid Arthritis in a Korean Population

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Human thymic stromal lymphopoietin receptor (TSLPR) might play an important role in the development of inflammatory and allergic responses. We previously identified eleven single nucleotide polymorphisms (SNPs) and two variation sites in the *TSLPR* gene and showed that all the SNPs of the *TSLPR* gene are associated with susceptibility to atopic asthma. The present study aimed to investigate whether the *TSLPR* gene SNPs are associated with susceptibility to rheumatoid arthritis (RA). We compared the genotype and the allele frequencies of the *TSLPR* SNPs in 457 RA patients and 570 healthy controls. The genotype and the allele frequencies of the *TSLPR* gene SNPs in the RA patients were not significantly different from the respective frequencies of the healthy controls. Additional analysis showed that the genotype and the allele frequencies of the *TSLPR* gene SNPs did not appear to be associated with RA in female RA patients. The *TSLPR* gene SNPs in the RA patients did not affect the production of rheumatoid factor (RF) and antisynthetic cyclic citrullinated peptide (CCP). Our results suggest that the *TSLPR* gene SNPs are not associated with susceptibility to RA in the Korean population.

Key words : Autoimmune disease, CRLF2, polymorphism, rheumatoid arthritis (RA), thymic stromal lymphopoietin receptor (TSLPR)

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases. RA comes about through the complex interaction between multiple genetic factors as well as environmental factors [8]. RA is characterized by inflammation of synovial tissues and the formation of rheumatoid pannus, which is capable of eroding adjacent cartilage and bone and causing subsequent joint destruction. A characteristic feature of RA is the presence of rheumatoid factors (RFs) and RF-containing immune complexes in both the circulation and synovial fluid [7]. RFs are auto-antibodies that recognize the Fc region of immunoglobulin G (IgG) antibodies and their isotypes. RF has been widely used as a screening test for patients with arthritis. RF is prognostically useful to correlates with functional [18] and outcomes in both RA and early inflammatory polyarthritis [9]. A highly specific auto-antibody system has been recently described for RA, in which the synthetic cyclic citrullinated peptide (CCP) with deiminated arginines is used as the antigen for the anti-CCP antibodies [14]. Anti-CCP antibodies are locally present at the site of inflammation in RA [13], and citrullinated proteins are found in the RA synovium [3].

Thymic stromal lymphopoietin (TSLP) has been proposed to signal through a heterodimeric receptor complex, which is composed of the TSLP receptor (TSLPR) and the IL-7R alpha chain [11, 12]. Human TSLP is involved in dendritic cell (DC) maturation [15, 19] and it is produced by epithelial cells, stromal cells and mast cells. We previously showed that the single nucleotide polymorphisms (SNPs) of TSLP were associated with the susceptibility to allergic rhinitis [22]. The human *TSLPR* gene is located on chromosome Xp22.3 and Yp11.3, and it consists of seven (NM_001012288.1, isoform 2) or eight exons (NM_022148.2, isoform 1). TSLPR contains two fibronectin type III-like domains, four conserved cysteine residues and a WSXWS (Trp-Ser-X-Trp-Ser) box-like motif that is typical for type I cytokine receptors. The C-terminal intracellular region contains a membrane-proximal Box 1 motif, which also functions as a putative binding site for signal transduction molecules [17, 23]. The TSLPR knockout mice have normal num-

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bers of lymphocytes, but the TSLPR/γ_c double knockout mice display a greater lymphoid defect than the γ_c KO mice [1]. Leonard and coworkers have also reported that these mice exhibit strong Th1 responses with high levels of interleukin (IL)-12, interferon-γ and immunoglobulin IgG2a, but low levels of IL-4, IL-5, IL-10, IL-13 and IgE [2]. TSLPR knockout mice fail to develop an inflammatory lung response to inhaled antigen unless they are supplemented with wild-type CD4$^+$ T cells [2]. These results indicated that TSLPR plays an important role in the development of inflammatory and/or allergic responses. Shi and coworkers have recently suggested that the local application of anti-TSLPR prevented Th2- mediated airway inflammation by regulating the function of DCs, and this might be exploited to develop novel treatments for asthma [16]. We previously identified eleven single nucleotide polymorphisms (SNPs) and two variation sites in human *TSLPR* gene, and suggested that the SNPs of the *TSLPR* gene were associated with the susceptibility to atopic asthma in the Korean population [21].

To determine whether the SNPs of the *TSLPR* gene are associated with the susceptibility of RA, we analyzed the allelic and genotypic frequencies between the RA patients and the healthy controls. We further investigated the relationships between the genotypes of each polymorphism and the anti-CCP antibody or RF levels in the RA patients. Finally, we calculated the haplotype frequencies that were constructed by these SNPs in both groups.

Materials and Methods

Patients and DNA samples

The DNA samples used in this study were provided by the Biobank of Wonkwang University Hospital, which is a member of the National Biobank of Korea and this Biobank is supported by the Ministry of Health, Welfare and Family Affairs. On the basis of approval and informed consent from the institutional review board, we obtained the genomic DNAs from 457 RA patients and 570 healthy controls. The clinical parameters of the study subjects are summarized in Table 1. Genomic DNA was extracted from the leukocytes in the peripheral blood by a standard phenol-chloroform method or by using a Genomic DNA Extraction kit (iNtRON Biotechnology, Sungnam, Korea) according to the manufacturer's directions. RA was diagnosed according to the criteria of the American Rheumatism Association. Anti-CCP antibody level in the RA patients was determined by enzyme-linked immunosorbent assay (ELISA) using DIASTAT anti-CCP antibody kit (MBL Co, Nagoya, Japan) and read by automated EIA analyzer, CODA (Bio-RAD Co, Tokyo, Japan). Anti-CCP antibody was considered positive when the absorbance was higher than the cut-off value (5 U/ml). The concentration of anti-CCP antibody was estimated by interpolation from a dose-response curve based on standards. RF level in the RA patients was measured by the latex fixation test using Hitachi 7170S (Hitachi Co, Tokyo, Japan). The cutoff for positivity was 18 IU/ml for RF. The non-rheumatoid arthritis healthy controls were recruited from the general population who underwent comprehensive medical testing at Wonkwang University Hospital. All the subjects in this study were Korean.

Table 1. Clinical characteristics of the study subject

	RA[a]	Control[a]
Number of subjects	457	570
Age (yr)	53.1±12.2	40.6±7.0
Gender (male/female)	87 / 370	356 / 214
Total IgE (IU/ml)	70.8±68.3	-
Anti-CCP antibody (U/ml)	49.5±46.1	-

[a]Data are means±standard deviation

Genotype analysis

Genotype analysis of the TSLPR SNPs were performed by high resolution melting (HRM) analysis (g.-43T>C, g.19646A>G and g.21995T>C), single-base extension (SBE) method (g.21884G>A), and Taq-man assay probes (g.33G>C and g.21869T>C) according to the previously described method [21]. The PCR cycling for HRM analysis was carried out using the Rotor-Gene thermal cycler RG6000 (Corbett Research, Sydney, Australia). The PCR cycling conditions were as follows; one cycle of 95°C for 15 min, 45 cycles of 95°C for 5 sec (g.-43T>C) or 15 sec (g.19646A>G and g.21995T>C), 58°C (g.21995T>C) or 60°C (g.-43T>C and g.19646A>G) for 10 sec and 72°C for 15 sec (g.-43T>C) or 30 sec (g.19646A>G and g.21995T>C). PCR for SBE analysis was performed with 50 ng each of genomic DNA and Taq DNA polymerase (Solgent, Daejeon, Korea) and 0.5 µM of each primer under the following conditions: 30 cycles of denaturation at 98°C for 10 sec, annealing at 55°C for 10 sec and extension at 72°C for 30 sec. The final extension was completed at 72°C for 10 min in a thermocycler (PE Applied Biosystem, Foster city, USA). The Taq-man assay probes for g.33G>C and g.21869T>C were designed by Integrated DNA

Technologies (IDT, Coralville, USA). FAM-fluorescence dye was attached to the TSLPR-1G, TSLPR-2T probe and the HEX-fluorescence dye was attached to the TSLPR-1C, TSLPR-2C probe [21]. The PCR conditions were as follows: one cycle at 95°C for 15 min, 50 cycles at 95°C for 15 sec and 64°C for 40 sec. The PCR was performed in the Rotor-Gene thermal cycler RG6000 (Corbett Research, Sydney, Australia). The samples were read and analyzed using the software Rotor-Gene 1.7.40 (Corbett Research, Sydney, Australia).

Statistic analysis

The RA patients and healthy controls were compared using case-control association analysis. χ^2 tests were employed to estimate the Hardy-Weinberg equilibrium (HWE). Pair-wise comparison of the biallelic loci was employed for the analyses of linkage disequilibrium (LD). The haplotype frequencies of TSLPR for multiple loci were estimated using the expectation maximization (EM) algorithm with SNPAlyze software (DYNACOM, Yokohama, Japan). Logistic regression analyses (SPSS 11.5) were used to calculate the odds ratios (with the 95% confidence intervals). The ANOVA method was applied to define the ANA levels of each genotype from the individual RA patients. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

Genotype analysis

To determine whether the *TSLPR* SNPs are associated

Table 2. Genotype and allele analyses of the *TSLPR* gene polymorphisms in RA patients and healthy controls

Position[a]	Genotype /Allele	Control n (%)	RA n (%)	Odds ratio[b] (95% CI)	P^c
g.-43T>C	TT	425 (76.6)	375 (83.0)	1.00	0.002
	TC	102 (18.4)	71 (15.7)	0.79 (0.57-1.10)	
	CC	28 (5.0)	6 (1.3)	0.24 (0.10-0.59)	
	T	952 (85.8)	821 (90.8)	1.00	0.001
	C	158 (14.2)	83 (8.2)	0.61 (0.46-0.81)	
g.33G>C	CC	520 (91.5)	396 (88.8)	1.00	0.124
	CG	48 (8.5)	48 (10.8)	1.31 (0.86-2.00)	
	GG	0 (0.0)	2 (0.4)	-	
	C	1088 (95.8)	840 (94.2)	1.00	0.100
	G	48 (4.2)	52 (5.8)	1.40 (0.94-2.10)	
g.19646A>G	GG	250 (44.2)	181 (40.9)	1.00	0.295
	GA	242 (42.7)	211 (47.6)	1.20 (0.92-1.57)	
	AA	74 (13.1)	51 (11.5)	0.95 (0.64-1.43)	
	G	742 (65.5)	573 (64.7)	1.00	0.707
	A	390 (34.5)	313 (35.3)	1.04 (0.86-1.25)	
g.21869T>C (rs36139698)	CC	408 (72.1)	333 (73.2)	1.00	0.510
	CT	147 (26.0)	109 (24.0)	0.91 (0.68-1.21)	
	TT	11 (1.9)	13 (2.9)	1.45 (0.64-3.27)	
	C	963 (85.1)	775 (85.2)	1.00	1.000
	T	169 (14.9)	135 (14.8)	0.99 (0.78-1.27)	
g.21884G>A (rs36177645)	AA	249 (44.5)	162 (37.9)	1.00	0.120
	AG	260 (46.4)	222 (52.0)	1.31 (1.01-1.71)	
	GG	51 (9.1)	43 (10.1)	1.30 (0.83-2.04)	
	A	758 (67.7)	546 (63.9)	1.00	0.084
	G	362 (32.3)	308 (36.1)	1.18 (0.98-1.43)	
g.21995T>C (rs36133495)	TT	204 (36.4)	163 (37.5)	1.00	0.864
	TC	274 (48.8)	205 (47.1)	0.94 (0.71-1.23)	
	CC	83 (14.8)	67 (15.4)	1.01 (0.69-1.48)	
	T	682 (60.8)	531 (61.0)	1.00	0.926
	C	440 (39.2)	339 (39.0)	0.99 (0.83-1.19)	

[a] Calculated from the translation start site

[b] Logistic regression analyses were used for calculating OR (95% CI; confidence interval)

[c] Value was determined by Fisher's exact test or χ^2 test from 2×2 contingency table

with the susceptibility of RA, the genotypes of the *TSLPR* SNPs, g.-43T>C (promoter), g.33G>C (exon 1), g.19646A>G (exon 7), g.21869T>C (rs36139698, exon 8), g.21884G>A (rs36177645, exon 8) and g.21995T>C (rs36133495, exon 8), were analyzed by the SBE, HRM or TaqMan probe method. Among the previously identified polymorphisms, these six SNPs were selected for genotyping analysis based on their locations and LD block. The genotypes and allele frequencies were compared between the RA patients and the healthy controls. All the genotype frequencies were in HWE, except for the g.-43T>C in the healthy controls (data not shown). The genotype and allele frequencies of *TSLPR* SNPs were not significantly different between the RA patients and healthy controls (Table 2). The *P* values in *TSLPR* SNPs (g.33G>C, g.19646A>G, g.21869T>C, g.21884G>A and g.21995T>C) were 0.124, 0.295, 0.510, 0.120 and 0.864, respectively. We further analyzed the genotype and allele frequencies between the females of the healthy control group and the RA patients because the RA patients were predominantly female compared with the healthy control subjects. The genotype and allele frequencies of the *TSLPR* SNPs were not significantly different between the female of the RA patients and the healthy controls (Table 3). These results suggest that the SNPs of the *TSLPR* gene could not be associated with the susceptibility to RA (Table 2, 3).

Quantitative traits analysis

On the other hand, to define a possible correlation be-

Table 3. Genotype and allele analyses of the polymorphisms of *TSLPR* gene polymorphisms in the female of RA patients and healthy controls

Position[a]	Genotype /Allele	Control n (%)	RA n (%)	Odds ratio[b] (95% CI)	*P*[c]
g.-43T>C	TT	161 (76.7)	306 (83.4)	1.00	0.0005
	TC	33 (15.7)	56 (15.3)	0.89 (0.56-1.43)	
	CC	16 (7.6)	5 (1.4)	0.16 (0.06-0.46)	
	T	355 (84.5)	668 (91.0)	1.00	0.0010
	C	65 (25.5)	66 (9.0)	0.54 (0.37-0.78)	
g.33G>C	CC	192 (90.6)	324 (89.3)	1.00	0.6873
	CG	20 (9.4)	38 (10.5)	1.13 (0.64-1.99)	
	GG	0 (0.0)	1 (0.3)	-	
	C	404 (95.3)	686 (94.5)	1.00	0.5860
	G	20 (4.7)	40 (5.5)	1.18 (0.68-2.04)	
g.19646A>G	GG	96 (45.7)	136 (37.9)	1.00	0.1782
	GA	92 (43.8)	183 (51.0)	1.40 (0.98-2.02)	
	AA	22 (10.5)	40 (11.1)	1.28 (0.72-2.30)	
	G	284 (67.6)	455 (43.4)	1.00	0.1569
	A	136 (32.4)	263 (36.6)	1.21 (0.94-1.56)	
g.21869T>C	CC	152 (72.0)	271 (73.4)	1.00	0.4916
	CT	56 (26.5)	88 (23.8)	0.88 (0.60-1.30)	
	TT	3 (1.4)	10 (2.7)	1.87 (0.51-6.90)	
	C	360 (85.3)	630 (85.4)	1.00	1.0000
	T	62 (14.7)	108 (14.6)	1.00 (0.71-1.40)	
g.21884G>A	AA	92 (44.2)	137 (39.4)	1.00	0.5273
	AG	99 (47.6)	181 (52.0)	1.23 (0.86-1.76)	
	GG	17 (8.2)	30 (8.6)	1.19 (0.62-2.27)	
	A	283 (68.0)	455 (65.4)	1.00	0.3939
	G	133 (32.0)	241 (34.6)	1.13 (0.87-1.46)	
g.21995T>C	TT	85 (40.3)	129 (36.3)	1.00	0.4700
	TC	99 (46.9)	169 (47.6)	1.13 (0.78-1.63)	
	CC	27 (12.8)	57 (16.1)	1.39 (0.82-2.37)	
	T	269 (63.7)	427 (60.1)	1.00	0.2310
	C	153 (36.3)	283 (39.9)	1.17 (0.91-1.50)	

[a] Calculated from the translation start site

[b] Logistic regression analyses were used for calculating OR (95% CI; confidence interval)

[c] Value was determined by Fisher's exact test or χ^2 test from 2×2 contingency table

tween the *TSLPR* SNPs and the clinical features of RA, we further analyzed the difference of the anti-CCP antibody and RF levels according to each genotype of the RA patients. We found that these SNPs in the RA patients have no significant association with the levels of RF and anti-CCP antibody (Table 4).

Haplotype analysis

Finally, we estimated the haplotype frequencies of the block 1 (g.-43T>C and g.33G>C) and the block 2 (g.21869T>C and g.21884G>A) of the *TSLPR* gene between the healthy controls and the RA patients (Table 5). Although the CG haplotype frequency was somewhat different in the block 2 of the RA patients, as compared to that of the healthy controls (p=0.016), the distributions of major haplotypes in block 1 and block 2 were not significant difference between the RA patients and the healthy controls. These results suggest that the haplotypes of the TSLPR polymorphisms are not associated with RA susceptibility.

Discussion

RA is one of the representative autoimmune diseases worldwide. This disease is arisen by the complex interaction between multiple genetic factors and environmental factors [8]. We previously suggested that the exon 4 variations of

Table 4. Analysis of RF and anti-CCP antibody levels among the each genotype of *TSLPR* gene SNPs in RA patients

Position[a]	Genotype	RF (1U/ml)			P^b	Anti-CCP antibody			P^b
		n	Mean	SD		n	Mean	SD	
g.-43T>C	TT	370	70.992	74.1	0.63	193	48.898	44.3	0.55
	TC	70	72.271	75.0		45	53.228	43.2	
	CC	5	103.00	90.7		2	-	-	
g.33G>C	CC	391	71.358	74.3	0.79	211	51.202	44.1	0.22
	CG	49	68.388	76.0		28	40.324	43.5	
	GG	2	-	-		2	-	-	
g.19646A>G	GG	179	68.207	75.2	0.58	90	52.085	43.4	0.62
	GA	209	74.359	74.3		114	46.906	45.4	
	AA	49	63.939	74.4		33	53.482	43.8	
g.21869T>C	CC	330	71.655	74.8	0.83	184	48.728	43.9	0.69
	CT	106	68.019	71.8		54	49.725	44.9	
	TT	13	61.615	79.8		6	64.350	49.5	
g.21884G>A	AA	159	72.654	75.9	0.56	81	48.945	44.8	0.89
	AG	220	70.300	74.1		131	50.986	44.1	
	GG	43	58.977	66.6		19	54.084	42.0	
g.21995T>C	TT	161	73.447	77.0	0.69	91	47.113	45.2	0.42
	TC	203	67.340	74.0		110	53.953	43.9	
	CC	66	73.667	71.2		35	45.029	41.8	

[a] Calculated from the translation start site.
[b] Values were analyzed by ANOVA

Table 5. The haplotype frequencies by *TSLPR* gene SNPs in RA patients and healthy controls

Haplotype			Frequency[a]		P^b
			Control	RA	
Block 1 (g.-43T>C, g.33G>C)	T	C	0.822	0.849	0.118
	C	C	0.135	0.093	0.003
	T	G	0.036	0.058	0.017
	C	G	0.007	3.0E-4	0.021
Block 2 (g.21869T>C, g.21884G>A)	C	A	0.675	0.640	0.099
	C	G	0.175	0.218	0.016
	T	G	0.147	0.141	0.717
	T	A	0.003	0.001	0.436

[a] Values were constructed by EM algorithm with genotyped SNPs
[b] Values were analyzed by permutation p-value

the *Tim-1* gene [4], the *eotaxin-3* polymorphisms [5] and the *TBX21* polymorphism [6] are associated with RA susceptibility.

Human TSLP is involved in dendritic cell maturation [15, 19] and it is produced by epithelial cells, stromal cells and mast cells. *TSLP* is highly expressed in bronchial epithelium and submucosa in allergic asthma [20], and also expressed in synovial fluid specimens derived from RA patients [10]. These results suggest that TSLP might be involved in allergic diseases as well as in inflammatory arthritis such as RA. TSLPR may be plays an important role in the development of inflammatory and/or allergic responses. The human TSLPR has been identified from a human T lymphocyte and dendritic cell (DC) cDNA library [17, 23]. We previously showed that the expressed levels of *TSLPR* mRNA by RT-PCR were highest in ovary, pancreas and lung, and they were only barely detected in kidney, heart, thymus and testis, while they were not detected in brain and skeletal muscle [21]. We also identified eleven SNPs and two variation sites in human *TSLPR* gene, and showed that the g.33G>C and g.19646A>G of the *TSLPR* gene were associated with the susceptibility to atopic asthma in the Korean population [21].

In this study, we analyzed the genotype of *TSLPR* SNPs in RA patients and healthy controls. The genotype and allele frequencies of *TSLPR* SNPs in RA patients were not significantly different from those in the healthy controls group (Table 2). This result suggests that the *TSLPR* SNPs not associated with the susceptibility to RA. Although the genotype and allele frequencies of g.-43T>C of *TSLPR* in RA patients were significantly different from those in the healthy controls group (Table 2, p=0.002 and 0.001, respectively), we exclude it because of the genotype frequencies of g.-43T>C in the healthy controls were not in HWE. The genotype and allele frequencies of the *TSLPR* SNPs were also not associated with the female RA patients (Table 3). These results suggest that the *TSLPR* SNPs may be not affected by the gender of RA patients.

The hallmarks of RA are RF and anti-CCP antibody; therefore further evaluation was made to see these SNPs have associations with RF and anti-CCP antibody levels in RA patients. The association levels were measured by ANOVA and compared the relationship. However there are no significant association between the RF and anti-CCP antibody levels and the genotype of *TSLPR* SNPs in RA patients (Table 4). These results suggest that the *TSLPR* SNPs are not affected to RF and anti-CCP antibody levels production in RA patients.

The distribution of the major haplotypes (TC in block 1, and CA in block 2) of the *TSLPR* SNPs in the RA patients was not different from the healthy controls (Table 5). These results suggest that the haplotypes of the *TSLPR* polymorphisms are not associated with RA susceptibility.

In conclusion, the results of this study suggest that *TSLPR* not associated with the pathogenesis of RA. However, we have still not comprehensively captured all the diversity in the *TSLPR* gene, and other associations may still reside at this locus; these associations could not be addressed in the present study. Our study has some limitations that the mean age of healthy controls are lower than that of RA patients. Although the mean age difference between the patient and healthy control groups, it might be not affected in the genetic results of this study.

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초록 : 한국인 류마티스 관절염의 감수성과 TSLPR 유전자 다형성의 연관성

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사람의 TSLPR는 염증 유발 및 알러지 반응에 중요한 역할을 한다. 우리는 TSLPR 유전자에서 11개의 유전자 다형성과 2개의 유전적 변이 부위를 발굴하였고, 이들 TSLPR 유전자 다형성이 아토피 천식의 민감성과 연관성이 있음을 확인 하였다. 이에 우리는 TSLPR 유전자 다형성과 류마티스 관절염과의 연관성에 대해서도 알아 보고자 하였다. 457명의 류마티스 관절염 환자군과 570명의 정상 대조군으로 TSLPR 유전자 다형성의 genotype과 allele frequencies를 비교 분석 해본 결과 두 그룹 간에 유의성이 없었고, 류마티스 관절염 여성 그룹에서의 비교 분석에서도 두 그룹 간에 유의성이 없었다. 또한, 류마티스 관절염 환자에서 TSLPR 유전자 다형성이 RF나 CCP levels에 영향을 미치지 않는 것으로 분석 되었다. 따라서, TSLPR 유전자 다형성이 한국인에서의 류마티스 관절염에 대한 민감성과 연관성이 없는 것으로 생각된다.