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Single Nucleotide Polymorphisms in Thymic Stromal Lymphopoietin Gene are not Associated with Aspirin-Exacerbated Respiratory Disease Susceptibility - A Pilot Study in a Japanese Population

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Abstract

Background: Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine, implicated in the development and progression of allergic diseases. Several studies indicated polymorphisms in TSLP gene were associated asthma, and two single nucleotides polymorphisms (SNPs) in TSLP (rs1837253 and rs2289276) were shown to be associated with asthma in a sex-specific fashion. However, there has been no report that investigated TSLP gene polymorphisms in patients with aspirin-exacerbated respiratory disease (AERD).

Methods: DNA specimens were obtained from the following three groups: 105 patients with AERD, 270 patients with aspirin-tolerant asthma (ATA) and 90 normal controls. The target DNA sequence of the TSLP gene was amplified using a set of primers. Allelic discrimination assay for the two SNPs in TSLP gene (rs1837253 and rs2289276) was carried out. All patients were Japanese, and they were in a stable condition.

Results: The frequency of the T minor allele of TSLP -5717C>T in patients with AERD and those with ATA was significantly higher than that in normal controls. There were no significant difference of the T minor allele frequency of TSLP -82C>T among the three groups. Analysis of genotype frequencies of the CT/TT genotype group and CC genotype both in TSLP -5717C>T and in TSLP -82C>T showed no differences between AERD and ATA patients. In addition, subgroup analysis of the genotype frequencies with gender did not differ between AERD and ATA patients.

Conclusion: This is the first pilot study to investigate TSLP gene polymorphisms in AERD, which didn't find an association between the TSLP gene polymorphisms and AERD susceptibility in a Japanese population, suggesting polymorphisms in TSLP gene may contribute to asthma, but not to aspirin hypersensitivity.

Keywords: Thymic stromal lymphopoietin; TSLP; Gene polymorphism; Aspirin-exacerbated respiratory disease; AERD; Bronchial asthma

Introduction

Aspirin-exacerbated respiratory disease (AERD), so-called aspirin-intolerant asthma, is a clinical syndrome characterized by aspirin hypersensitivity and severe asthmatic attack after taking aspirin and/or nonsteroidal anti-inflammatory drugs (NSAIDs), and the pathogenesis of AERD has been suggested to be caused by arachidonic acid metabolites such as leukotrienes (LTs) [1]. The inhibitory action of aspirin and NSAIDs on cyclooxygenase activity may cause diversion to the 5-lipoxygenase pathway, which reads to the overproduction of cysteinyl LTs [1,2]. Therefore, genetic association studies of LT-related genes have been undertaken to explore the genetic determinants of AERD. LTC4 synthase promoter polymorphism was reported to be associated with AERD [3,4]. Also, the genetic polymorphisms of 5-lipoxygenase promoter [5] and cysteinyl LT receptor 1 promoter [6] were shown to influence the susceptibility to AERD as risk factors. However, conflicting results have been reported [7,8], indicating that in parallel with replication studies in different ethnic groups, future areas of investigation should focus on the identification of genetic biomarkers for early diagnosis of AERD. In fact, we have reported some new genetic aspects in Japanese patients with AERD from our laboratory [9-14].

Thymic stromal lymphopoietin (TSLP) is produced from several cells, including epithelial cells, stromal and muscular cells [15-17]. TSLP drives allergic inflammatory responses through its activity on a number of innate immune cells, including dendritic cells [18, 19], mast cells [20], and $CD34^+$ progenitor cells [21]. Levels of human TSLP messenger RNA [22,23] and protein [23] have been reported to be increased in the airways of patients with asthma, as compared with controls, and the magnitude of this expression correlate with the severity of disease [22,23].

The gene for TSLP is located on human chromosome 5q22, near the gene cluster encoding Th2 cytokines [24]. A sex-stratified analysis showed that a single nucleotide polymorphism (SNP) (rs2289276) in TSLP gene was associated with cockroach-specific IgE in Costa Rican

female [25]. Several studies have shown an association between SNPs in the human TSLP gene and asthma as follows. In a large Canadian population, a SNP (rs1837253) 5.7 kb upstream of the TSLP transcription start site was associated with asthma [26] and the association was replicated in a large consortium study [27]. Two SNPs in TSLP gene (rs1837253 and rs2289276) were also shown to be associated with asthma in a sex-specific fashion in Costa Rican population [28]. The genome-wide association studies identified TSLP gene as a susceptibility loci associated with asthma [29]. TSLP promoter polymorphisms were shown to be associated with disease susceptibility in both childhood atopic and adult asthma in Japanese population [30]. These data suggest that differential regulation of TSLP expression may influence on susceptibility to bronchial asthma.

To our knowledge, no studies have evaluated the gene association of TSLP with AERD in any independent population. Therefore, taking all into account, we hypothesize that TSLP gene polymorphism might be involved in the susceptibility of AERD, and we have expanded our studies in this paper. Based on the reports mentioned above, two SNPs in TSLP gene (rs1837253 and rs2289276) were tested in this study. This is the first pilot study analyzing TSLP-5717C>T and -82C>T gene polymorphisms in patients with AERD in a Japanese population.

Materials and Methods

Subjects

This study was approved by the institutional review board at each clinical site in Japan, and was conducted in conformance with the ethical principles on the Declaration of Helsinki, Good Clinical Practices, and applicable local regulations. Written informed consent was obtained from each patient before study procedures were initiated.

All subjects were non-smoking Japanese and were recruited from the outpatient clinic of Sutoh Hospital, Yukawa Clinic of Internal Medicine, and Hiroshima Allergy and Respiratory Clinic, Japan. Smoking habit was ascertained by means of a questionnaire. One hundred and two patients with AERD in this study were already included in the analysis of our recent study [13]. Characteristics of the study population are shown in Table 1.

	AERD	ATA	NC
Number of subjects	105	270	90
Age (years)	51.9 ± 13.7	50.2 ± 13.6	46.9 ± 19.8
Gender (male)	27 (25.7%)	89 (33.0%)	32 (35.6%)
FEV1 (% predicted)	73.7 ± 11.3	75.5 ± 24.5	NA
Serum IgE(IU/mL)[b]	263.5 ± 526.0	329.8 ± 396.7	NA
Eosinophil (cells/μL)[c]	677.0 ± 787.1	292.4 ± 304.3	NA

Table 1: Clinical characteristics of the subjects in the study[a].

AERD: Aspirin-Exacerbated Respiratory Disease; ATA: Aspirin-Tolerant Asthma; FEV1: Forced Expiratory Volume in One Second; NC: Normal Controls; NA: Not Applicable.

[a]Data are presented as means ± SD or numbers (%).

[b]P<0.001 for AERD patients versus ATA patients by the Welch's t-test.

[c]P<0.001 for AERD patients versus ATA patients by the Welch's t-test.

Diagnosis of bronchial asthma was confirmed using the Global Initiative for Asthma guidelines [31]. All patients showed clinical symptoms that met the criteria for asthma, such as cough, wheeze and shortness of breath, and they were diagnosed by experienced pulmonologists. Forced expiratory volume in one second (FEV1) was measured with a spirometer, and airway reversibility was defined as a >12 % and >200 ml increase in volume in the first second of forced expiration from baseline after inhalation of short-acting β2-adrenergic bronchodilators. The diagnosis of AERD was made on the basis of either a positive result on lysine-aspirin challenge test [4] or an apparent history of more than one self-reported episode of bronchial response to aspirin or NSAID ingestion. The provocation test could not be applied to the subjects who didn't give written informed consent mainly because of the risk of significant occult disease, although the likelihood of severe reaction was considered very low. Aspirin-tolerant asthma (ATA) was defined as bronchial asthma with no history of NSAID-induced asthma attack. Non-smoking subjects with no history of bronchial asthma or other respiratory symptoms were selected from healthy volunteers who visited our clinic for annual routine physical examinations, and comprised normal controls. The serum levels of total IgE were measured by the CAP system (Phadia, Uppsala, Sweden). The total eosinophil count was measured in peripheral blood using a flow cytometer (Coulter Maxm; Beckman-Coulter Inc., Fullerton, CA, USA).

Genotyping of TSLP gene polymorphism

DNA in the specimens obtained by rubbing buccal mucosa by a cotton swab was extracted by using QIAamp 96 DNA blood kits (Qiagen, Hilden, Germany). The target DNA sequence of TSLP -5717C>T was amplified using a set of primers (forward: 5'-GGTTACTTTGTAAAAGATCC-3', reverse: 5'-CTCTATTGTGTAATT TGCTTC-3'). The target DNA sequence of TSLP -82C>T was amplified using a set of primers (forward: 5'-CTCTGGAGCATCAGGGAGAC-3', reverse: 5'-CAATTCCACC-CCAGTTTCAC-3'). Allelic discrimination assay for two SNPs relating to the expressions of TSLP -5717C > T and TSLP -82C>T (rs1837253 and rs2289276, respectively) was carried out by using previously described SNPs detective system, sequence-specific thermal-elution chromatography [9-14]. All subjects and investigators remained unaware of the genotype until the final analysis.

Statistical analysis

Data are presented as means ± SD or numbers (%) of observations, unless stated otherwise. Differences in the mean value of the phenotypic characteristics within the groups were compared using either ANOVA test or t-test, and qualitative data were compared by the Chi-square test. Allele frequencies were estimated by gene counting method. Significant departures of genotype frequency from the Hardy-Weinberg equilibrium at each SNP were tested by the Chi-square analysis. Differences in minor allele T frequency of TSLP-5717C>T and TSLP-82C>T in patients with AERD and ATA were compared with that in control subjects by means of the Chi-square test. Each gene polymorphism related to the asthma phenotype was examined by multivariable logistic regression models with adjustment for covariates, namely with the asthma phenotype as dependent variable and independent variables including age (continuous value), gender (male=0, female=1), two alternatives

genotype models that were combined heterozygous CT and homozygous TT genotype group and homozygous CC genotype. In addition, subgroup analyses with gender of the multivariable logistic regression analysis were performed. Statistical analyses were undertaken using SPSS for Windows version 17 (SPSS Inc, Chicago, IL, USA). P-values of <0.05 were considered to be significant.

The study design of our investigation is summarized in Figure 1.

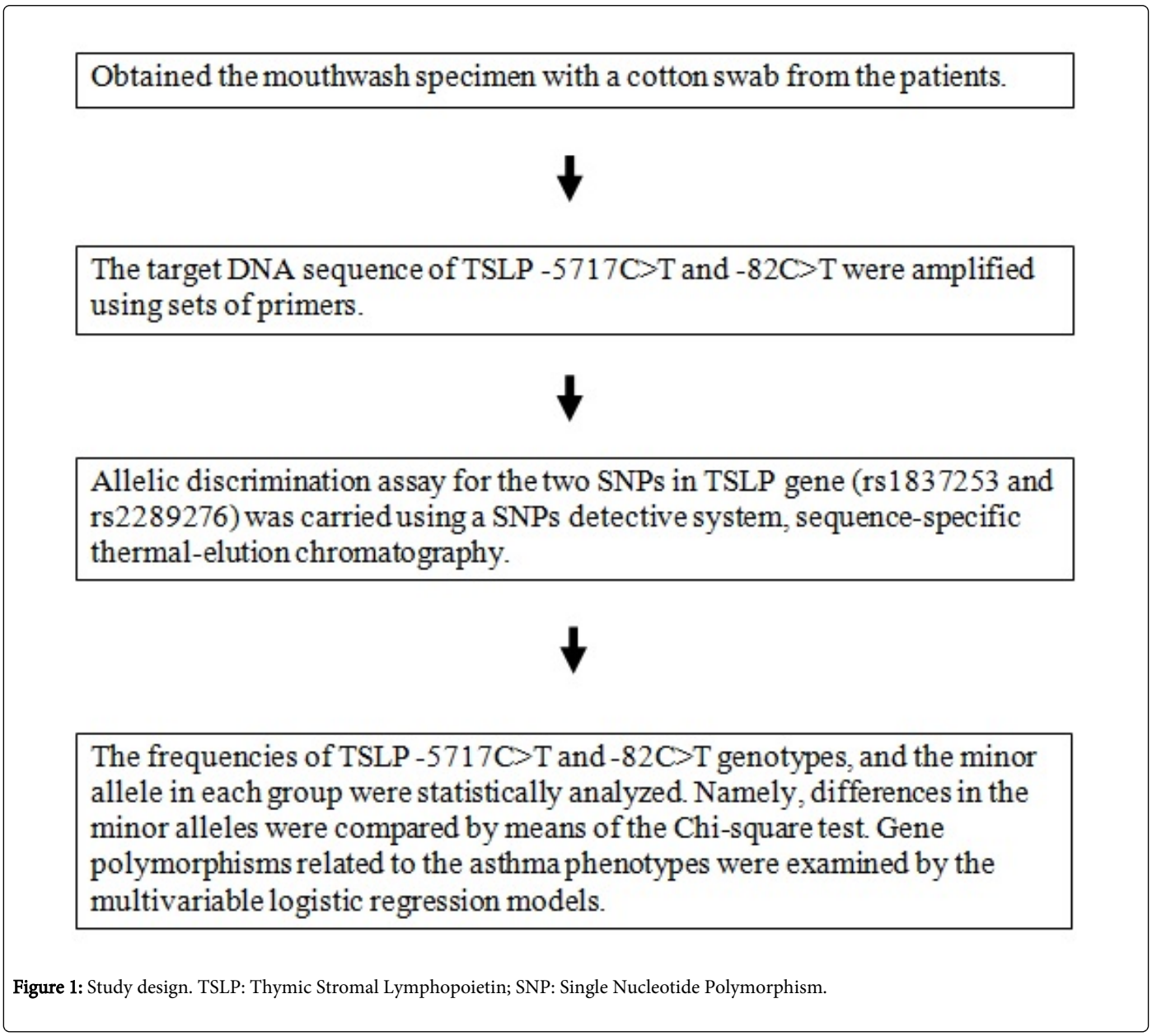

Figure 1: Study design. TSLP: Thymic Stromal Lymphopoietin; SNP: Single Nucleotide Polymorphism.

Results

Table 1 shows the clinical characteristics of the subjects. There was no significant difference between AERD patients and ATA patients in terms of age, number of male patients and FEV1 (% predicted). The levels of total serum IgE in AERD patients were significantly lower than that in ATA patients (P<0.001). AERD patients had a higher peripheral total eosinophil count compared with ATA patients (P<0.001).

The frequencies of TSLP-5717C>T and TSLP-82C>T genotype, and the T minor allele in each group are shown in Table 2. The genotype distribution of the TSLP gene fulfills the Hardy-Weinberg equilibrium in each group. The frequencies of the T minor allele of TSLP-5717C>T in patients with AERD (frequency of allele [q]=0.390) and those with ATA (q=0.340) were similar, and did not differ between them. The frequency of the minor T allele of TSLP-5717C>T genotype in patients with AERD was significantly higher than that in normal controls (q=0.244) (P=0.002). Also, the frequency of the minor T allele of TSLP-5717C>T genotype in patients with ATA was significantly higher than that in normal controls (P=0.020). On the other hand, the frequency of the minor T allele of TSLP-82C>T genotype did not differ among AERD patients, ATA patients and normal controls groups.

SNP loci	Genotype, No. (%)			Allele	P-value	HWE
	CC	CT	TT	Frequency	P-Value	
-5717C>T						
AERD	15	52	38	0.390	**0.002**	0.697
(n=105)	(14.3%)	(49.5%)	(36.2%)			
ATA	25	132	113	0.340	**0.020**	0.122
(n=270)	(9.3%)	(48.9%)	(41.9%)			
NC	7	30	53	0.244	-	0.355
(n=90)	(7.8%)	(33.3%)	(58.9%)			
-82C>T						
AERD	55	42	8	0.276	0.604	0.996
(n=105)	(52.4%)	(40.0%)	(7.6%)			
ATA	136	116	18	0.281	0.634	0.307
(n=270)	(50.4%)	(43.0%)	(6.7%)			
NC	43	40	7	0.300	-	0.581
(n=90)	(47.8%)	(44.4%)	(7.8%)			

Table 2: Genotype and allele frequencies of the TSLP gene in each group.

AERD: Aspirin-Exacerbated Respiratory Disease; ATA: Aspirin-Tolerant Asthma; NC: Normal Controls; HWE: Hardy-Weinberg Equilibrium. Minor alleles in patients with AERD and patients with ATA were compared with that in control subjects by means of the Chi-square test. Values in bold indicate significant P-value.

The results of multivariable logistic regression analysis of TSLP-5717C>T and TSLP-82C>T genotype controlling age and gender in patients with AERD compared with those with ATA are shown in Table 3 - (A). Frequencies of homozygous CC genotype of TSLP-5717C>T were not different from those of combined homozygous TT and heterozygous CT genotype group in patients with AERD compared with those with ATA (P=0.179), and the odds ratio (OR) of patients with AERD compared with those with ATA associated with homogenous CC genotype of TSLP-5717C>T to those with combined homozygous TT and heterozygous CT genotype group was 1.604 (95 % confidence interval (CI)=0.805-3.196). Frequencies of homozygous CC genotype of TSLP-82C>T were not different from those of combined homozygous TT and heterozygous CT genotype group in patients with AERD compared with those with ATA (P=0.651), and the OR of patients with AERD associated with homozygous CC genotype to those with combined homozygous TT and heterozygous CT genotype group compared with ATA was 1.111 (95 % CI=0.704-1.752).

Table 3 - (B) represents subgroup analyses with gender of the TSLP gene. No positive association was present between asthma phenotype and TSLP-5717C>T genotype both in male (P=0.496, OR=1.552, 95% CI=0.437-5.510) and in female (P=0.255, OR=1.613, 95% CI=0.708-3.675). Also, no positive association was present between asthma phenotype and TSLP-82C>T genotype both in male (P=0.507, OR=0.746, 95% CI=0.314-1.774) and in female (P=0.320, OR=1.315, 95% CI=0.766-2.258).

(A)		
SNP loci	**Genotype**	**OR (95% CI), P-value**
-5717C>T	CT/TT	1.000
	CC	1.604 (0.805-3.196), 0.179
-82C>T	CT/TT	1.000
	CC	1.111 (0.704-1.752), 0.651
(B)		
SNP loci	**Male**	**Female**
Genotype	OR (95% CI), P-value	OR (95% CI), P-value
-5717C>T		
CT/TT	1.000	1.000
CC	1.552(0.437-5.510), 0.496	1.613(0.708-3.675), 0.255
-82C>T		
CT/TT	1.000	1.000
CC	0.746(0.314-1.774), 0.507	1.315(0.766-2.258), 0.320

Table 3: Multivariable logistic regression analysis (A) and the subgroup analysis with gender (B) of genotype of the TSLP gene in Japanese patients with AERD compared with those with ATA.

OR: Odds Ratio; CI: Confidence Interval.

Multivarible logistic regression analysis was applied for age and gender (A) and age (B) as covariables.

Discussion

AERD is known to be associated with higher peripheral blood eosinophil count and less atopic tendency than ATA [1], which correspond to the results in this investigation. We recently reported an advance in investigation of gene polymorphisms in Japanese patients with AERD, and suggested potential genetic biomarkers contributing to the early diagnosis of AERD [14]. We've extended our investigations to explore the genetic determinations of AERD in this study.

We investigated the genotype and allele frequencies of TSLP-5717C>T and -82C>T in three groups (AERD patients, ATA patients and normal controls). The frequency of the minor T allele of TSLP-5717C>T genotype in patients with ATA was significantly higher than that in normal controls (P=0.020), and this result corresponds to the reports which showed evidence for association of a TSLP variant (rs1837253) with asthma [26,27]. Interestingly, the frequency of the minor T allele of TSLP-5717C>T genotype in patients with AERD was also significantly higher than that in normal controls (P=0.002). The frequency of the minor T allele of TSLP-82C>T genotype did not differ among the three groups (AERD patients, ATA patients and normal controls). Analysis of the frequencies of the combined TT and CT genotype group and CC genotype showed no significant differences in the genotype frequencies between AERD patients and ATA patients both in TSLP-5717C>T and TSLP-82C>T genotypes. Overall, these findings suggest that the TSLP gene may present itself as a good candidate involved in the development of asthma, however it is unlikely to be associated with susceptibility to AERD in Japanese subjects.

AERD is well known to be associated with higher female incidence [1]. On the other hand, it has been reported that TSLP gene polymorphisms were associated with asthma in a sex-specific fashion in Costa Rican population [28]. Namely, the T allele of rs1837253 was significantly associated with a reduced risk of asthma in males only, whereas the T allele of rs2289276 was significantly associated with a reduced risk of asthma in females only [28], suggesting gender might modify the role of TSLP in asthma. So, subgroup analyses with gender of the multivariable logistic regression analysis were performed using the two SNPs (rs1837253 and rs2289276) in the present study. However, the frequencies of the combined TT and CT genotype group and CC genotype in these SNPs showed no difference between AERD patients and ATA patients both in TSLP-5717C>T and -82C>T genotypes in Japanese population.

The present study has certain limitations. First, the number of the study subjects was limited. Secondarily, patients with AERD were diagnosed by experienced pulmonologists, and the diagnosis of AERD was made on the basis of either a positive result on lysine-aspirin challenge test [4] or an apparent history of more than one self-reported episode of bronchial response to aspirin or NSAID ingestion, indicating it may dilute the sample size with risk of including false positive patients. However, one hundred and two patients with AERD in this study were already included in the analysis of our recent study [13], which showed the gene association of heat shock protein 70 with AERD. In this study, a good number of the patients with AERD were recruited from the outpatient clinics of the experienced Japanese pulmonologists.

In the present study, the relation between the genotyping and clinical findings in patients with AERD could not be demonstrated. Nevertheless, it is easy to speculate that a single genetic factor cannot explain the genetic background of AERD, and therefore, other factors conferring susceptibility of AERD remain to be identified.

In conclusion, we were the first to analyze TSLP-5717C>T and TSLP-82C>T gene polymorphisms in patients with AERD, and this pilot study could not show an association between two SNPs in the TSLP gene region and AERD susceptibility in Japanese subjects, suggesting TSLP-5717C>T and -82C>T gene sequence variations may not have a role in the development of AERD. The findings of our pilot study were based on small-sized samples from Japanese population, and further validation studies in independent population, such as another Asian, Caucasian, Hispanic/Latino and African American, are thus required.

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