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Human *IL-27p28* Gene Polymorphisms are Associated with the Serum Total IgE Levels of Allergic Rhinitis Patients

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Interleukin 27 (IL-27) was discovered as a heterodimeric cytokine of the IL-12 family, and is composed of two subunits - Epstein-Barr virus induced gene 3 (EBI3) and p28. It acts as a versatile cytokine in the early regulation of Th1 initiation and in the negative regulation of the Th2 factor GATA binding protein 3 (GATA-3). This cytokine is mediated by the IL-27 receptor (WSX-1), which is highly expressed on $CD4^+$ T lymphocytes and NK cells. We previously identified four polymorphisms in the human *IL-27p28* gene and suggested that the polymorphism of *IL-27p28* is associated with susceptibility to asthma. To determine whether these *IL-27p28* SNPs are associated with susceptibility to allergic rhinitis, the genotype and allele frequencies of *IL-27p28* SNPs were analyzed between allergic rhinitis patients and healthy controls. Although the genotype and allele frequencies of *IL-27p28* SNPs in allergic rhinitis patients were not significantly different from those of the control group, there was a suggestive difference (P=0.037) between these groups in total serum IgE levels in the *g.2905T>G* SNP of the *IL-27p28* gene. Our result implies that the *g.2905T>G* SNP of the *IL-27p28* gene might have an affect on IgE production in allergic rhinitis patients.

Key words : Interleukin 27 (IL-27), polymorphism, haplotype, allergic rhinitis, IgE

Introduction

Allergic rhinitis is a multi-complex inflammatory disorder of the nasal mucosa. It is characterized by predominance of Th2 cytokines and IgE production, and recruitment of mast cells, eosinophils and basophils to the site of allergic reactivity [6,12]. Naïve T helper cells are differentiated into T helper 1 (Th1) cell or Th2 cells depending on multiple influences by cytokines, types of antigen, transcription factors and signaling pathways [9]. However, genetic polymorphisms may be one of the more crucial factors that predisposing to the imbalance between Th1 and Th2 cells. Th1 cells release cytokines IL-2, IFN-γ, TNF-β, and Th2 cells produce IL-4, IL-5 and IL-10. Binding of the cytokines to their target receptors results in activation of transcription factors involved in signaling pathways [9]. The balance between Th1 and Th2 is very important in maintaining the healthy state of the body [9]. Overproduction of Th1 cytokines has been implicated in auto-immune diseases, and aberrant regulation of the Th2-type response is associated with allergic inflammation.

Interleukin 27 (IL-27) recently has been determined to be a novel heterodimeric cytokine of the IL-12 family. IL-27 is composed of two subunits. One is a soluble type I cytokine receptor-like molecule, from Epstein-Barr virus (EBV)-induced gene 3 (EBI3), and the other subunit is p28 [7,14]. They are highly co-expressed in LPS-activated monocytes and monocyte-derived dendritic cells (DCs) of human [14]. Structurally, the heterodimeric IL-27p28 chain belongs to the family of long-chain 4-helix bundle cytokines and displays sequence homology to *IL-12p35* and *IL-23p19* [14]. The IL-27 receptor (IL-27R) is composed of class I cytokine receptor chain WSX-1 (also known as TCCR) and cytokine IL-6 related gp130 chain [15,16]. The biological effects of IL-27 are mediated by the WSX-1 that is highly expressed on $CD4^+$ T lymphocytes and NK cells. IL-27 is known to play multiple roles in the up-regulation of Th1 initiation as well as in the down-regulation of Th2 factor Gata binding protein 3 (GATA-3). In comparison with wild-type mice, WSX-$1^{(-/-)}$ mice reveals significantly increased levels of airway immune response and serum IgE with infiltration of pulmonary eosinophil. That indicates IL-27 and WSX-1 have a function in the down-regulation of airway hyper-re-

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activity and lung inflammation during the development of allergic asthma [11].

Although, *IL-27p28* is one of the crucial candidate genes for the development and differentiation of T cells, a correlation between single nucleotide polymorphisms (SNPs) of *IL-27p28* and individual susceptibility of allergic rhinitis has no information. We previously identified four polymorphisms in the human *IL-27p28* gene and suggest that the *g.-964A>G* SNP of *IL-27p28* probably associated with susceptibility to asthma [1]. Moreover, the haplotype frequencies of *g.2905T>G*, *g.4603G>A* and *g.4730T>C* are elucidated with specific correlation between the asthma patients and the healthy controls. To determine whether these *IL-27p28* SNPs are associated with susceptibility of allergic rhinitis, we have analyzed their frequencies on the genomic DNAs isolated from the allergic rhinitis patients and the healthy controls. We also analyzed the haplotype frequencies by these SNPs between the allergic rhinitis patients and the healthy controls. Finally, we investigated the relationships between individual allergic rhinitis patients and the polymorphisms by measuring total serum IgE levels and by counting peripheral blood eosinophil numbers.

Materials and Methods

Patients and DNA samples

On the basis of approval and informed consent from the review board of School of Medicine, Wonkwang University, blood samples were obtained from 447 healthy controls (281 males and 166 females) and 289 allergic rhinitis patients (186 males and 103 females). The mean ages of controls and patients were 38.8 years and 23.8 years respectively. Genomic DNA was extracted from leukocytes in peripheral blood by a standard phenol-chloroform method or by Genomic DNA Extraction kit (iNtRON Biotechnology, Seongnam, Korea) according to the manufacturer's directions. The allergic rhinitis patients were recruited from the outpatient clinic of Wonkwang University Hospital. The diagnosis was based on symptoms of sneezing, watery rhinorrhea, nasal obstruction, and the result of a positive skin test. The skin test was performed with six common aeroallergens from house dust mites, house dust, grass mix, tree pollens, animal dander, and molds (Torii; Tokyo, Japan). All of the patients with allergic rhinitis had a history of the symptoms and had a positive skin test. The controls were recruited from the general population who took a comprehensive medical examination at Wonkwang University Hospital. All subjects in this study were Korean and were living in the same area.

Polymerase chain reaction (PCR)

The entire coding regions of *IL-27P28,* including 1.9 kb promoter regions, were partially amplified with using GeneAmp PCR system 9700 thermocycler (PE Applied Biosystem, USA) and three primer pairs [1]. The PCR was carried out in a total reaction volume of 20 μl containing 50 ng genomic DNA, 0.5 μM primers, 0.2 mM dNTP, 1.5 mM $MgCl_2$, 10 mM TRIS-HCl (pH 8.3), and one unit of EF Taq polymerase (Solgent, Korea). The reactions were carried out at 94°C for 5 min, followed by 30 cycles at 98°C for 10 sec, at 68°C for 30 sec and at 72°C for 2 min. The final extension was completed at 68°C for 7 min. After purification using PCR purification kit (Millipore, USA), the PCR products were employed as a template DNA for genotyping analysis.

Single-base extension (SBE)

Genotyping for *g.-964A>G*, *g.2905T>G* and *g.4730T>C* in the *IL-27P28* gene was performed by single-base extension (SBE) with ABI Prism® SNaPshot™ Multiplex kit (Applied Biosystems). The PCR products purified by PCR purification kit (Millipore, USA) were used as the template DNA for three SBE primers [1]. The SBE reaction mix was prepared according to previously described method [3]. The primer extension reaction was performed at 96°C for 1 minute, followed by 25 cycles at 96°C for 10 sec, at 55°C for 40 sec, and at 60°C for 30 sec. To clean up the primer extension reaction, 1 unit of CIP (New England BioLabs) was added to the reaction mixture and incubated at 37°C for 60 minutes. Extension reaction was terminated at 72°C for 15 min. The purified extension products were added to Hi-Di formamide (Applied Biosystems) and incubated at 95°C for 5 min, followed by 5 min on ice, then electrophoresis was performed using ABI Prism 3100 Genetic Analyzer. For the analysis of sequencing results, ABI Prism GeneScan and Genotyper software (Applied Biosystems) were employed.

Statistic analysis

The χ^2 tests were applied to estimate the Hardy-Weinberg equilibrium (HWE). Pair-wise comparison of biallelic loci was employed for the analyses of Linkage Disequilibrium (LD). The haplotype frequencies of *IL-27P28* for multiple loci were estimated using the expectation maximization (EM) al-

gorithm with SNPAlyze software (DYNACOM, Japan). Logistic regression analyses were adapted to calculate odds ratios (95% confidence interval). For statistic analysis, ANOVA method was applied to define IgE levels of each genotype and to count the number of peripheral blood eosinophil from individual asthma patients. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results

We previously identified four SNPs, *g.-964A>G* (rs153109), *g.2905T>G* (novel SNP), *g.4603G>A* (rs181207) and *g.4730T>C* (rs181206), in human *IL-27p28* gene, and suggested that the *g.-964A>G* polymorphism of *IL-27p28* associated with susceptibility to asthma [1]. To determine whether these *IL-27p28* SNPs are associated with susceptibility of allergic rhinitis, the genotype and allele frequencies of *IL-27p28* polymorphisms were analyzed between the allergic rhinitis patients and the healthy controls. The genotypes of *IL-27p28* SNPs were determined in 447 unrelated healthy controls and in 289 unrelated allergic rhinitis patients by SBE method. All genotype frequencies of these SNPs were in Hardy-Weinberg equilibrium (HWE) by χ^2 tests (data not shown).

The genotype frequencies of *g.-964A>G*, *g.2905T>G* and *g.4730T>C* were not significantly different between the allergic rhinitis patients and the healthy controls (P = 0.557, 0.470 and 0.003, respectively). The allele frequencies of *g.-964A>G*, *g.2905T>G* and *g.4730T>C* also were not significantly different between two groups (Table 1). Total serum IgE levels and peripheral blood eosinophil counts, among each genotype of these SNPs, were compared among allergic rhinitis patients. The SNPs of allergic rhinitis patients have no significant correlation with the peripheral blood eosinophil counts (Table 2). Although the total serum IgE levels in the *g.-964A>G* and *g.4730T>C* of *IL-27p28* gene were no significant association, the total serum IgE levels in the *g.2905T>G* SNP of *IL-27p28* gene was significantly different (P=0.037, Table 2). This result suggests that the *g.2905T>G* SNP of *IL-27p28* gene might be affect on the IgE production in allergic rhinitis patients.

On the other hand, to define a possible correlation between the haplotypes by *IL-27p28* SNPs and the susceptibility of allergic rhinitis, we also evaluated the haplotype frequencies by these SNPs in both healthy controls and allergic rhinitis patients (Table 3). Four major haplotypes were identified explaining more than 95.3% and 99.2% of distribution in controls and allergic rhinitis patients, respectively, out of eight possible haplotypes. Although the frequency of major haplotype (ATT) was not significantly different in both the healthy controls and the allergic rhinitis patients (65.8% and 66.1%, respectively), the frequency of

Table 1. Genotype and allele analyses of the polymorphisms of *IL-27p28* gene in allergic rhinitis patients and healthy controls

Position[a]	Genotype / Allele	Control n (%)	AR n (%)	Odds ratio[b] (95% CI)	P^c
g.-964A>G (rs153109)	AA	216 (48.6)	130 (45.3)	1.00	0.557
	AG	190 (42.8)	127 (44.3)	1.11 (0.81-1.51)	
	GG	38 (8.6)	30 (10.4)	1.31 (0.78-2.22)	
	A	622 (70.0)	387 (67.4)	1.00	0.298
	G	266 (30.0)	187 (32.6)	1.13 (0.90-1.42)	
g.2905T>G	TT	343 (80.0)	231 (82.5)	1.00	0.470
	TG	79 (18.4)	47 (16.8)	0.88 (0.59-1.32)	
	GG	7 (1.6)	2 (0.2)	0.42 (0.09-2.06)	
	T	765 (89.2)	509 (90.9)	1.00	0.323
	G	93 (10.8)	51 (9.1)	0.82 (0.58-1.18)	
g.4730T>C (rs181206)	TT	336 (77.6)	228 (81.1)	1.00	0.135
	TC	96 (22.2)	50 (17.8)	0.77 (0.52-1.12)	
	CC	1 (0.2)	3 (1.1)	4.42 (0.46-42.8)	
	C	768 (88.7)	506 (90.0)	1.00	0.433
	T	98 (11.3)	56 (10.0)	0.87 (0.61-1.23)	

[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.

Table 2. Analysis of serum total IgE levels and peripheral eosinophil counts among the genotypes of each SNP of *IL27p28* in allergic rhinitis patients

Position[a]	Genotype	Eosinophil[b]			P^c	IgE (IU/ml)			P^c
		n	Mean	SD		n	Mean	SD	
g.-964A>G	AA	97	0.409	0.308	0.47	35	698	696	0.25
	AG	99	0.381	0.343		35	506	551	
	GG	25	0.471	0.294		15	417	530	
g.2905T>G	TT	177	0.410	0.351	0.66	63	660	678	0.037
	TG	39	0.384	0.238		19	323	257	
	GG	2	-	-		2	-	-	
g.4730T>C	TT	177	0.415	0.348	0.57	71	575	625	0.30
	TC	39	0.357	0.248		13	387	372	
	CC	3	0.330	0.197		1	-	-	

[a]Calculated from the translation start site.
[b]Values were determined by the eosinophil numbers ($10^3/\mu l$).
[c]Values were analyzed by ANOVA.

Table 3. The haplotype frequencies by the SNPs of *IL27p28* gene in allergic rhinitis patients and healthy controls

Haplotype			Frequency[a]		χ^2	P^b
g.-964A>G	g.2905T>G	g.4730T>C	Control	AR		
A	T	T	0.658	0.661	0.019	0.913
G	T	T	0.120	0.148	2.108	0.157
G	T	C	0.091	0.098	0.195	0.658
G	G	T	0.084	0.085	0.003	0.963
A	G	T	0.024	0.006	6.076	0.036
A	T	C	0.022	0.002	9.870	0.002
others			0.001	0.000	-	-

[a]Values were constructed by EM algorithm with genotyped SNPs.
[b]Values were analyzed by permutation test.

minor AGT haplotype (2.4% and 0.6%, respectively) and minor ATC haplotype (2.2% and 0.2%, respectively) were significantly different between the healthy controls and allergic rhinitis patients group (P=0.036 and 0.002, respectively).

Discussion

Allergic diseases such as allergic rhinitis, asthma and atopic dermatitis are usually happened by an excessive immune response to certain antigens called allergens. Allergic rhinitis could be initiated by the common allergens, such as pollen, house dust and mites, in atopic individuals. A series of cellular interactions on exposure to specific allergens ultimately resulted in the inflammation of nasal mucosa which is accompanied by elevation of serum IgE levels and recruitment of eosinophil to the site of allergic reactivity [13]. The several numbers of studies have been reported for analyzing the association of SNPs with allergic rhinitis. Cheng and coworkers reported that the polymorphisms of disintegrin and metalloprotease domain 33 (*ADAM33*) gene are associated with susceptibility to allergic rhinitis in Japanese population [5]. The polymorphisms of *IL-13* were also associated with susceptibility of allergic rhinitis, and they were accountable for the high level of IgE in allergic rhinitis patients [17]. We previously reported, the polymorphisms of *eotaxin-2* and *eotaxin-3*, interleukin 28 receptor A (*IL-28RA*) and forkhead-box J1 (*FOXJ1*) are associated with allergic rhinitis in Korean population [2,4,10].

The allergic disorders usually accompanied by increased level of IgG1 and IgE on the activation of eosinophil and mast cells [8]. The IL-27 composed of two subunits, EBI3 and p28, is one of the vital cytokines that mediates between the innate and adaptive immune system. The IL-27 and WSX-1 plays an important role in the down-regulation of airway hyper-reactivity and lung inflammation during the development of allergic asthma through its suppressive ef-

fect on cytokine production [11]. We previously identified four SNPs in human *IL-27p28* gene, and suggested that the *IL-27p28* polymorphisms are possibly correlated with susceptibility to asthma [1]. In this study, we analyzed the genotype and allele frequencies at three SNPs of *IL-27p28* gene between the allergic rhinitis patients and the healthy controls, and found that the genotype and allele frequencies of SNPs in *IL-27p28* gene were not significantly different between the allergic rhinitis patients and the controls group (Table 1). This result suggests the *IL-27p28* SNPs are not associated with susceptibility to allergic rhinitis.

Although the *IL-27p28* gene polymorphisms in the allergic rhinitis patients have no significant association with the peripheral blood eosinophil counts, it was shown that the total serum IgE levels between the healthy controls and the allergic rhinitis patients were significantly different in the *g.2905T>G* SNP of *IL-27p28* gene (Table 2). This suggests that the *IL-27p28* polymorphism (*g.2905T>G*) is probably one of the most crucial genetic factors in serum IgE production. Actually, the *g.2905T>G* SNP is located on the exon 2 of *IL-27p28* gene, and a single nucleotide transition T to G resulted in amino acid change to p.Ser59Ala. Whereas the frequency of major haplotype (ATT) was not significantly different in the healthy controls and the allergic rhinitis patients, the frequency of minor haplotypes (AGT and ATC) in the allergic rhinitis patients were significantly different than that of the control group (Table 3). This result indicates that the haplotypes by *IL-27p28* polymorphisms is not important genetic factors in allergic rhinitis susceptibility.

Taken as a whole, our results suggest that the *g.2905T>G* SNP in *IL-27p28* gene would be associated with total serum IgE production, but not with the peripheral blood eosinophil counts, and with susceptibility to allergic rhinitis. Although it is not clear that how can *IL-27p28* act in serum IgE production, our results could provide an insight to further functional studies of *IL-27p28* in association with allergic responses.

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초록 : 사람의 IL-27p28 유전자 다형성은 알레르기성 비염 환자 혈청의 IgE 양과 연관됨

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인터루킨 27(IL-27)은 인터루킨 12계열의 이성이량체 사이토카인으로 EBI3와 p28의 두 서브유니트로 구성 되어 있다. 인터루킨 27은 Th1 개시의 초기 조절에 관여하는 사이토카인으로 Th2 인자인 GATA-3의 작용을 억제하는 역할을 한다. 이 사이토카인은 $CD4^+$ T 림프구와 자연살해세포에서 아주 높게 발현하는 수용체(WSX-1)에 의하여 매개된다. 우리들은 사람의 IL-27p28유전자에서 네 개의 유전자다형성 부위를 찾아서 이들 유전자다형성이 기관지 천식의 감수성에 영향을 미치는 것을 보고한 바 있다. 이 연구에서는 IL-27p28 유전자의 유전자다형성이 알레르기성 비염의 감수성에 영향을 미치는 지를 알아보기 위하여 이들 다형성에 있어서 알레르기성 비염환자 군과 정상인 군 사이의 유전자형 및 대립형질의 빈도를 비교분석 하였다. 비록 알레르기성 비염환자 군에서 IL-27p28 유전자의 유전자다형성의 유전자형 및 대립형질의 빈도의 차는 정상인 군의 그것과 큰 차이가 없었으나, g.2905T>G SNP에서 두 그룹간에 주목할만한 차이(P=0.037)를 발견하였다. 이 결과는 IL-27p28 유전자의 g.2905T>G 유전자 형성이 알레르기성 비염환자에서 IgE의 생산에 영향을 준다는 것을 암시한다.