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Association of the Human IL-28RA Gene Polymorphisms in a Korean Population with Asthma

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Abstract

IL-28RA is one of the important candidate genes for complex trait of genetic diseases, but there are only a few published results for this gene. Previously, we identified eighteen SNPs and two variation sites in the entire coding regions of *IL-28RA* including promoter regions, and suggested that the g.32349G>A polymorphism of *IL-28RA* might be associated with susceptibility to allergic rhinitis. In this study, we chose seven SNPs (*g.-1193A>C, g.-30C>T, g.17654C>T, g.27798A>G, g.31265C>T, g.31911C>T* and *g.32349G>A*) of *IL-28RA*, and attempted to find out whether these polymorphisms were furtherassociated with genetic predisposition of asthma. We analyzed the genotype and allele frequencies of *IL-28RA* polymorphisms between the asthma patients and healthy controls. We also investigated the frequencies of haplotype constructed by these SNPs between asthma patients and controls. Our results suggest that the polymorphisms of *IL-28RA* gene were not associated with susceptibility to asthma, and not with IgE production and eosinophil recruitment. The haplotype frequencies by these SNPs also not significantly associated between the healthy controls and asthma patients. This result indicates that the *IL-28RA* polymorphisms might be not associated withasthma susceptibility.

Keywords: IL-28RA, polymorphism, haplotype, asthma, cytokine

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Introduction

Asthma is one of the most common multi-complex disorders that triggered by genetic predisposition and environmental factors (Cookson, 2002). Unlike other inflammatory diseases, the asthmatic inflammatory process is characterized by the predominant secretion of interleukin (IL)-4 and IL-5 by T-helper lymphocyte type 2 (Th2) and immunoglobulin E (IgE) synthesis.IgE mediates early and late asthmatic responses in an induction of lung eosinophil infiltration and Th2 cell cytokine production (Coyle *et al.*, 1996). Mast cells are IgE-dependently activated, while eosinophils and basophils are recruited into the site of allergic reaction (Daser *et al.*, 1995; O'Garra, 1998). The accumulation of eosinophils is an important characteristicfeature in the pathogenesis of asthma, because it accompanied by inflammation within the bronchial wall (Humbles *et al.*, 1997).

Cytokines are multifunctional proteins that mediate many of responses of innate and adaptive immunities. They are produced in response to microbes, antigens, and other cytokines and stimulatediverse responses of cells involved in immunity and inflammation. They act on target cells by binding to specific cytokine receptor, initiating signal transduction and second signal pathways within the target cell (Hibi and Hirano, 1998; Onishi *et al.*, 1998; O'Shea *et al.*, 2002). The SNPs of many cytokines and their receptor genes, such as *IL-10, IL-12, IFNγ, RANTES, CCR2* and *CCR5*, are identified (Gibson *et al.*, 2001; Hall *et al.*, 2000; Iwasaki *et al.*, 2001) and indicate that the polymorphisms are associated with immune disorders (Fryer *et al.*, 2000; Nakao *et al.*, 2001). We previously reported that the polymorphisms of eotaxin gene family (eotaxin, eotaxin-2 and eotaxin-3) and the exon 4 variation of Tim-1 are associated with asthma in Korean population (Chae *et al.*, 2003; Chae *et al.*, 2004).

The new cytokine family consisting of interleukin 28A (IL-28A; also designated as IFN-γ2), IL-28B (IFN-γ3) and IL-29 (IFN-γ1) and a component of their receptors, IL-28RA (IFN-γR1), are identified from the human genomic sequence (Dumoutier *et al.*, 2003; Kotenko *et al.*, 2003; Sheppard *et al.*, 2003). They are distantly related to type I interferons (IFNs) and the IL-10 family, and induced by viral infection and show antiviral activity (Sheppard *et al.*, 2003; Kotenko *et al.*, 2003). However, IL-28 and IL-29

interact with a heterodimeric class II cytokine receptor that consist of IL-10 receptor β (IL-10Rβ) and an orphan class II receptor chain, designated IL-28RA. Recently, Dumoutier and co-workers suggested that IL-29 induced STAT2 tyrosine phosphorylation is mediated through tyrosines 343 and 517 of the IL-28RA and these two tyrosines are also responsible for antiviral and anti- proliferative activities of IL-29. In contrast, STAT4 phosphorylation is independent from IL-28RA tyrosine residues (Dumoutier *et al.*, 2004). IL-28RAgenes are located on the chromosomal region 1p36.11 and have seven exons.

More recently, we identified eighteen SNPs and two variation sites in human *IL-28RA* gene and reported that the *g.32349G>A* polymorphism of *IL-28RA* might be associated with susceptibility to allergic rhinitis (Chae *et al.*, 2006). In an attempt to better understand the genetic influences of *IL-28RA* on allergic disease such as asthma, we analyzed the genotype frequencies of the SNPs in *IL-28RA* in the genomic DNAs isolated from asthma patients and healthy controls to determine whether these *IL-28RA* SNPs are associated with asthma susceptibility. We further investigated the relationships among these polymorphisms to IgE levels and peripheral blood eosinophil counts in asthma patients.

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 280 asthma patients (146 males and 134 females) and 559 healthy non-asthma controls (346 males and 213 females). The mean ages of asthma patients and healthy controls were about 50.5 and 40.8 years respectively. Genomic DNA was extracted from leukocytes of peripheral blood by a standard phenol- chloroform method or by Genomic DNA Extraction kit (iNtRON Biotechnology, Korea) according to manufacturer's directions. The asthma (atopic and non-atopic) patients were recruited from our outpatient clinic at Chonbuk National University Hospital. Asthma was diagnosed in reference to the criteria of the American Thoracic Society (American Thoracic Society, 1987). The healthy controls were recruited from the general population and had undergone a comprehensive medical screening at the Wonkwang University Hospital. All subjects employed in this study were Korean who is living in the same area. Blood eosinophil counts and total serum IgE levels in asthma patients were measured, at the Department of Hematology of Chonbuk National University Hospital, using a Coulter GenSTM Hematology Analyzer (Florida, USA) and Roche COBAS-CORE II (Roche Diagnostics, Basal, Switzerland), respectively.

Polymerase chain reaction (PCR)

The entire coding regions of *IL-28RA* including ~2.0 kb promoter regions were partially amplified by PCR using the six primer pairs, and PCR reactions were prepared by previously described condition (Chae *et al.*, 2006). Amplification was carried out in a GeneAmp PCR system 9700 thermocycler (PE Applied Biosystem, USA) at 94°C for 2 minutes, followed by 10 cycles at 94°C for 10 seconds, 68°C or 45 seconds (2 minutes for promoter and exon 1 region, and 4 minutes for exon 7 and 3′ UTR region), and 68°C for 10 minutes. Then 20 cycles at 94°C for 10 seconds, 68°C for 45 seconds and 68°C or 10 minutes (with 10 seconds incremental increases per cycle) were followed by a final extension at 68°C for 7 minutes.

Single-base extension (SBE)

Genotyping for g.*-1193A>C, g.-30C>T, g.17654C>T, g.27798A>G, g.31265C>T, g.31911C>T* and *g.32349G>A* in the IL-28RA gene was performed by single-base extension (SBE) method (Chae *et al.*, 2006) using the ABI Prism® SNaPshot™ Multiplex kit (Applied Biosystems). The PCR products purified by PCR purification kit (Millipore, USA) were used as the template DNA for genotyping. The SBE reaction mix was prepared according to previously described method (Chae *et al.*, 2005). The primer extension reaction was performed at 96°C for 1 minute, followed by 25 cycles at 96°C for 10 seconds, 55°C for 40 seconds, and 60°C for 30 seconds. To clean up the primer extension reaction, 1.5 unit of CIP (Promega) was added to the reaction mixture, and the mixture was incubated at 37°C for 90 minutes, followed by 15 minutes at 72°C for purposes of enzyme inactivation. The purified extension products were added to Hi-Di formamide (Applied Biosystems) according to the recommendations of the manufacturer. The mixture was incubated at 95°C for 5 minutes, followed by 5 minutes on ice, and then electrophoresis was performed, using the ABI Prism 3100 Genetic Analyzer. The results were analyzed using the ABI Prism GeneScan and Genotyper software (Applied Biosystems).

Statistic analysis

The allergic rhinitis patients and non-allergic rhinitis controls were compared using case-control association analyses. The x^2 tests were used to estimate the Hardy-Weinberg equilibrium (HWE). Logistic regression analyses

were used to calculate odds ratios (95% confidence interval) for SNP sites. Linkage Disequilibrium (LD) analyses by pair-wise comparison of biallelic loci and the haplotype frequencies of *IL-28RA* for multiple loci were estimated using the expectation maximization (EM) algorithm with SNPAlyze software (DYNACOM, Japan). The haplotype analyses of *IL-28RA* SNPs between asthma patients and control were performed by Permutation test. A *P*-value of less than 0.05 was considered to indicate statistical significance.

Results and Discussion

In response to different cytokine profiles, T helper cells are classified into Th1 and Th2 subsets. Th1 cells secrete cytokines (including IFN-γ, IL-2 and TNF-β) and they join in the elimination of intracellular pathogens. On the other hand, Th2 cells produce IL-4, IL-5, IL-10 and IL-13. Eventually, they promote antibody production and control extracellular pathogens (Ho and Glimcher, 2002). Th1/Th2 balance is very important in maintaining the healthy state of body. When the balance is altered, some disorders (such as asthma and RA) would occur. Th1 and Th2 cells can mutually antagonize the differentiation of the counterpart subset (Lafaille *et al.*, 1997). *IL-28RA* is recently identified from the human genomic sequence as a component of their receptors for the new cytokine consisting of *IL-28A, IL-28B* and *IL-29* (Sheppard *et al.*, 2003; Kotenko *et al.*, 2003). Although *IL-28RA* is one of the important candidate genes for complex trait of genetic diseases, there are only a few published results for this gene. Previously, we identified eighteen SNPs and two variation sites in the entire coding regions of *IL-28RA* including promoter regions, and suggested that the *g.32349G>A* polymorphism of *IL-28RA*

Table 1. Genotype and allele analyses of the polymorphisms of *IL-28RA* gene in asthma patients and controls

Position	Genotype/ allele	Control n (%)	Asthma n (%)	Odds ratio[b] (95% CI)	P[c]
g.-1193A>C	AA	462 (82.7)	225 (80.9)	1.00	
	AC	93 (16.6)	48 (17.3)	1.06 (0.72-1.55)	0.344
	CC	4 (0.7)	5 (1.8)	2.57 (0.68-9.65)	
	A	1017 (91.0)	498 (89.6)	1.00	0.376
	C	101 (9.0)	58 (10.4)	1.17 (0.84-1.65)	
g.-30C>T	CC	88 (15.8)	33 (11.9)	1.00	
	CT	274 (49.0)	132 (47.7)	1.29 (0.82-2.02)	0.192
	TT	197 (35.2)	112 (40.4)	1.52 (0.96-2.41)	
	C	430 (38.5)	198 (35.7)	1.00	0.284
	T	688 (61.5)	356 (64.3)	1.12 (0.91-1.39)	
g.17654C>T	CC	453 (82.5)	242 (86.4)	1.00	
	CT	93 (16.9)	35 (12.5)	0.70 (0.46-1.07)	0.182
	TT	3 (0.6)	3 (1.1)	1.87 (0.38-9.35)	
	C	999 (91.0)	519 (92.7)	1.00	0.263
	T	99 (9.0)	41 (7.3)	0.80 (0.55-1.17)	
g.27798A>G	AA	99 (17.8)	55 (20.0)	1.00	
	AG	272 (49.0)	126 (45.8)	0.83 (0.56-1.23)	0.634
	GG	184 (33.2)	94 (34.2)	0.92 (0.61-1.39)	
	A	470 (42.3)	236 (42.9)	1.00	0.833
	G	640 (57.7)	314 (57.1)	0.98 (0.80-1.20)	
g.31265C>T	CC	49 (9.5)	27 (11.0)	1.00	
	CT	232 (44.9)	118 (48.0)	0.92 (0.55-1.55)	0.468
	TT	236 (45.6)	101 (41.1)	0.78 (0.46-1.31)	
	C	330 (31.9)	172 (35.0)	1.00	0.244
	T	704 (68.1)	320 (65.0)	0.87 (0.70-1.09)	
g.31911C>T	CC	348 (65.8)	159 (64.6)	1.00	
	CT	170 (32.1)	80 (32.5)	1.03 (0.74-1.43)	0.792
	TT	11 (2.1)	7 (2.8)	1.39 (0.53-3.66)	
	C	866 (81.9)	398 (80.9)	1.00	0.673
	T	192 (18.1)	94 (19.1)	1.07 (0.81-1.40)	
g.32349G>A	GG	216 (40.8)	101 (41.1)	1.00	
	GA	241 (45.5)	119 (48.4)	1.06 (0.77-1.46)	0.436
	AA	73 (13.8)	26 (10.6)	0.76 (0.46-1.26)	
	G	673 (63.5)	321 (65.2)	1.00	0.532
	A	387 (36.5)	171 (34.8)	0.93 (0.74-1.16)	

[a] Calculated from the translation start site.
[b] Logistic regression analyses were used for calculating OR (95% CI; confidence interval)
[c] Value was determined byFisher's exact test or $\chi 2$ test from 2 × 2 contingency table

Table 2. Genotype and allele analyses of the polymorphisms of *IL-28RA* gene in atopic (ato) or non-atopic (non-ato) asthma patients and controls

Position[a]	Genotype	Control n (%)	Asthma		P[b]	
			Atopic n (%)	Nonatopic n (%)	vs. ato	non-ato
g.-1193A>C	AA	462 (82.7)	75 (78.1)	37 (80.4)	0.561	0.752
	AC	93 (16.6)	20 (20.8)	9 (19.6)		
	CC	4 (0.7)	1 (1.1)	0 (0.0)		
	A	1017 (91.0)	170 (88.5)	83 (90.2)	0.285	0.850
	C	101 (9.0)	22 (11.5)	9 (9.8)		
g.-30C>T	CC	88 (15.8)	15 (15.6)	4 (8.5)	0.693	0.397
	CT	274 (49.0)	43 (44.8)	26 (55.3)		
	TT	197 (35.2)	38 (39.6)	17 (36.2)		
	C	430 (38.5)	73 (38.0)	34 (36.2)	0.936	0.741
	T	688 (61.5)	119 (62.0)	60 (63.8)		
g.17654C>T	CC	453 (82.5)	80 (82.5)	42 (84.0)	0.279	0.857
	CT	93 (16.9)	15 (15.5)	8 (16.0)		
	TT	3 (0.6)	2 (2.0)	0 (0.0)		
	C	999 (91.0)	175 (90.2)	92 (92.0)	0.687	0.856
	T	99 (9.0)	19 (9.8)	8 (8.0)		
g.27798A>G	AA	99 (17.8)	22 (23.9)	11 (22.4)	0.383	0.634
	AG	272 (49.0)	42 (45.7)	21 (42.9)		
	GG	184 (33.2)	28 (30.4)	17 (34.7)		
	A	470 (42.3)	86 (46.7)	43 (43.9)	0.296	0.831
	G	640 (57.7)	98 (53.3)	55 (56.1)		
g.31265C>T	CC	49 (9.5)	9 (10.7)	5 (11.9)	0.631	0.766
	CT	232 (44.9)	33 (39.3)	20 (47.6)		
	TT	236 (45.6)	42 (50.0)	17 (40.5)		
	C	330 (31.9)	51 (30.4)	30 (35.7)	0.721	0.469
	T	704 (68.1)	117 (69.6)	54 (64.3)		
g.31911C>T	CC	348 (65.8)	59 (70.2)	29 (69.0)	0.681	0.889
	CT	170 (32.1)	23 (27.4)	12 (28.6)		
	TT	11 (2.1)	2 (2.4)	1 (2.4)		
	C	866 (81.9)	141 (83.9)	70 (83.3)	0.588	0.883
	T	192 (18.1)	27 (16.1)	14 (16.7)		
g.32349G>A	GG	216 (40.8)	42 (50.0)	17 (40.5)	0.238	0.933
	GA	241 (45.5)	34 (40.5)	20 (47.6)		
	AA	73 (13.8)	8 (9.5)	5 (11.9)		
	G	673 (63.5)	118 (70.2)	54 (64.3)	0.099	0.907
	A	387 (36.5)	50 (29.8)	30 (35.7)		

[a] Calculated from the translation start site.
[b] Value was determined by Fisher's exact test or x^2 test from 2×2 contingency table

might be associated with susceptibility to allergic rhinitis, but seems to have no relationship with serum total IgE levels. The haplotype frequencies by these SNPs also show significant association between controls and allergic rhinitis patients.

In our present study, we attempted to find out whether these polymorphisms of *IL-28RA* were further associated with genetic predisposition of another allergic disease such as asthma. We analyzed the genotype and allele frequencies of *IL-28RA* polymorphisms between the asthma patients and healthy controls. The genotype frequencies of all loci were in HWE ($P>0.05$, data not shown). The genotype and allele frequencies of polymorphisms in asthma patients were not significantly different from those in the controls group (Table 1). This result suggests the polymorphisms of *IL-28RA* are not associated with susceptibility to asthma. We further analyzed the genotype and allele frequencies of atopic asthma, non-atopic asthma patients and healthy controls. In both atopic and non-atopic asthma patients, the genotype and allele frequencies of *IL-28RA* polymorphism, were not significantly different from the frequencies of healthy control group (Table 2). This result indicates that the polymorphism of *IL-28RA* might be not associated with susceptibility of atopic disease.

Eosinophil is accumulated in high numbers in the lungs of asthmatic patients and is believed to be essential in phagocytosis as well as in allergic and inflammatory reactions of asthma. Therefore, the number of accumulated eosinophils

Table 3. The levels of IgE, eosinophil counts, FVC and FEV1 among the genotypes of polymorphisms of *IL-28RA* gene in asthma patients

Positiona	Genotype	Eosinophil (%)			P[b]	IgE (IU/ml)			P[b]	FVC (%)			P[b]	FEV1 (%)			P[b]
		n	Mean	SD		n	Mean	SD		n	Mean	SD		n	Mean	SD	
	AA	200	4.90	5.28		213	262	199		190	70.3	21.2		191	65.6	27.5	
g.-1193A>C	AC	41	5.33	7.53	0.65	46	253	188	0.65	42	67.8	23.0	0.73	42	64.5	26.9	0.84
	CC	4	2.60	2.72		3	361	256		3	65.3	15.1		3	56.7	11.6	
	CC	28	5.12	4.82		30	299	189		27	71.6	18.3		27	67.9	23.7	
g.-30C>T	CT	113	4.79	6.86	0.93	121	240	192	0.20	110	67.7	23.9	0.35	110	63.0	29.6	0.49
	TT	104	5.04	4.37		111	276	204		98	71.7	19.1		90	67.1	25.4	
	CC	212	4.85	5.94		227	271	248		204	69.1	21.5		205	64.8	27.5	
g.17654C>T	CT	34	5.88	4.16	0.33	34	275	189	0.94	32	69.6	18.6	0.90	32	61.2	24.1	0.49
	TT	2	-	-		2	-	-		2	-	-		2	-	-	
	AA	47	4.91	4.30		51	255	193		49	68.2	19.7		49	61.1	23.2	
g.27798A>G	AG	111	4.89	4.59	0.99	120	269	199	0.87	107	69.6	21.4	0.85	107	64.6	28.0	0.42
	GG	85	5.02	7.52		87	258	200		77	70.4	22.9		78	67.7	29.3	
	CC	27	6.05	8.78		25	321	186		22	65.4	20.5		22	61.5	27.6	
g.31265C>T	CT	108	4.53	4.28	0.45	111	277	201	0.15	98	69.4	20.0	0.48	99	65.5	26.5	0.78
	TT	94	4.90	5.74		96	241	194		91	71.4	23.6		91	66.1	28.9	
	CC	146	4.47	5.08		152	260	194		139	71.2	21.9		139	66.4	28.1	
g.31911C>T	CT	76	5.56	6.50	0.37	73	269	204	0.19	66	67.0	21.7	0.43	67	62.7	27.2	0.58
	TT	7	5.47	4.22		7	399	153		6	70.2	13.0		6	71.3	20.6	
	GG	94	4.90	5.74		96	241	194		91	71.4	23.6		91	66.1	28.9	
g.32349G>A	GA	109	4.62	4.36	0.66	112	276	200	0.12	98	69.4	20.0	0.48	99	65.5	26.5	0.78
	AA	26	5.73	8.79		24	328	187		22	65.4	20.5		22	61.5	27.6	

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

Table 4. The haplotype frequencies by *IL-28RA* polymorphisms in asthma patients and controls

Haplotype				Frequency[a]		χ^2	P[b]
g.-30C>T	g.17654C>T	g.27798A>G	g.32349G>A	Control	Asthma		
T	C	G	G	0.203	0.187	0.496	0.565
T	C	A	G	0.171	0.225	6.409	0.039
T	C	G	A	0.158	0.166	0.141	0.754
C	C	G	A	0.114	0.151	4.094	0.137
C	C	A	G	0.111	0.109	0.026	0.923
C	C	G	G	0.085	0.059	3.296	0.178
T	C	A	A	0.050	0.021	7.196	0.067
C	T	A	G	0.031	0.011	5.435	0.102
T	T	A	G	0.021	0.050	9.861	0.023
C	C	A	A	0.020	0.004	5.737	0.219
Others				0.036	0.017	-	-

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

within the bronchial wall is a characteristic feature of asthma (Humbles *et al.*, 1997). At least, a dozen of polymorphic genes have been estimated that regulate asthma by controlling the inflammatory response, total serum immunoglobulin E (IgE), cytokines and chemokines (Cookson, 1999). However, our results reveal the polymor phisms of *IL-28RA* gene in asthma patients are not closely associated with the level of total serum IgE, the peripheral blood eosinophil count, FVC and FEV_1 (Table 3). We also calculated the haplotype frequencies among *g.-30C>T, g.17654C>T, g.27798A>G* and *g.32349G>A* in both healthy controls and asthma patients. While the most major haplotype (20.3% of distributions) in healthy control was TCGG, the most major haplotype (22.5% of distributions) was TCAG in asthma patients (Table 4). The distribution of haplotype TCAG and TTAG were significantly different between the controls and asthma patients (*P=0.039* and *P = 0.023*, respectively). But the frequency of haplotype TTAG was low in both group, and the haplotype TCAG corrected by bonferroni correction also not significantly associated. These results suggest that the haplotype frequencies by these SNPs also not significantly associated between the healthy controls and

asthma patients.

In this study, our results suggest that the polymorphisms of *IL-28RA* gene were not associated with susceptibility to asthma, and not with IgE production and eosinophil recruitment. The haplotype frequencies by these SNPs also not significantly associated between controls and asthmapatients. Our study is the first analysis about *IL-28RA* SNPs in asthma, and may contribute to the future study on the *IL-28RA* functions and association studies with other allergic, atopic or infectious disease.

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References

American Thoracic Society. (1987). Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am. Rev. Respir. Dis.* 136, 225-245.

Chae, S.C., Lee, Y.C., Park, Y.R., Shin, J.S., Song, J.H., Oh, G.J., Hong, S.T., Pae, H.O., Choi, B.M., and Chung, H.T. (2004). Analysis of the polymorphisms in eotaxin gene family and their association with asthma, IgE and eosinophil. *Biochem. Biophys. Res. Commun.* 320, 131-137.

Chae, S.C., Park, Y.R., Li, C.S., Lee, J.H., Yang, Y.S., Zhang, Q., Kim, K.S., and Chung, H.T. (2006). Analysis of the variations in *IL-28RA* gene and their association with allergic rhinitis. *Experimental and Molecular Medicine* 38, 302-309.

Chae, S.C., Park, Y.R., Song, J.H., Shim, S.C., Yoon, K.S., and Chung, H.T. (2005). The polymorphisms of Tim-1 promoter region are associated with rheumatoid arthritis in a Korean population. *Immunogenetics* 56, 696-701.

Chae, S.C., Song, J.H., Lee, Y.C., Kim, J.W., and Chung H.T. (2003). The association of the exon 4 variations of Tim-1 gene with allergic diseases in a Korean population. Biochem. *Biophys. Res. Commun.* 312, 346-350.

Cookson, W. (2002). Genetics and genomics of asthma and allergic diseases. *Immunol. Rev.* 190, 195-206.

Cookson, W. (1999).The alliance of genes and environment in asthma and allergy. *Nature* 25, 6760.

Coyle, A.J., Wagner, K., Bertrand, C., Tsuyuki, S., Bews, J., and Heusser, C. (1996). Central role of immunoglobulin (Ig) E in the induction of lung eosinophil infiltration and T helper 2 cell cytokine production: inhibition by a non-anaphylactogenic anti-IgE antibody. *J. Exp. Med.* 183, 1303-1310.

Daser, A., Meissner, N., Herz, U., and Renz. H. (1995). Role and modulation of T-cell cytokines in allergy. *Curr. Opin. Immunol.* 7, 762-770.

Dumoutier, L., Lejeune, D., Hor, S., Fickenscher, H., and Renauld, J.C. (2003). Cloning of a new type II cytokine receptor activating signal transducer and activator of transcription (STAT) 1, STAT2 and STAT3. *Biochem. J.* 370, 391-396.

Dumoutier, L., Tounsi, A., Michiels, T., Sommereyns, C., Kotenko, S.V., and Renauld, J.C. (2004). Role of the interleukin (IL)-28 receptor tyrosine residues for antiviral and antiproliferative activity of IL-29/interferon-lambda 1: similarities with type I interferon signaling. *J. Biol. Chem.* 279, 32269-32274.

Fryer, A.A., Spiteri, M.A., Bianco, A., Hepple, M., Jones, P.W, Strange, R.C., Makki, R., Tavernier, G., Smilie, F.I., Custovic, A., Woodcock, A.A., Ollier, W.E, and Hajeer, A.H. (2000) The -403 G→ promoter polymorphism in the RANTES gene is associated with atopy and asthma. *Genes Immun.* 1, 509-514.

Gibson, A.W., Edberg,J.C., Wu, J., Westendorp, R.G., Huizinga, T.W., and Kimberly, R.P. (2001). Novel single nucleotide polymorphisms in the distal IL-10 promoter affect IL-10 production and enhance the risk of systemic lupus erythematosus. *J. Immunol.* 166, 3915-3922.

Hall, M.A., McGlinn, E., Coakley, G., Fisher, S.A., Boki, K., Middleton, D., Kaklamani, E., Moutsopoulos, H., Loughran, T.P., Jr, Ollier, W.E., Panayi, G.S., and Lanchbury, J.S. (2000). Genetic polymorphism of IL-12 p40 gene in immune-mediated disease. *Genes Immun.* 1, 219-224.

Hibi, M., and Hirano, T. (1998). Signal transduction through cytokine receptors. Int. *Rev. Immunol.* 17, 75-102.

Ho, I.C. and Glimcher, L.H. (2002). Transcription: tantalizing times for T cells. *Cell* 109, S109-S120.

Humbles, A.A, Conroy, D.M., Marleau, S., Rankin, S.M., Palframan, R.T., Proudfoot, A.E., Wells, T.N., Li, D., Jeffery, P.K., Griffiths-Johnson, D.A., Williams, T.J., and Jose, P.J. (1997). Kinetics of eotaxin generation and its relationship to eosinophil accumulation in allergic airways disease: analysis in a guinea pig model *in vivo*. *J. Exp. Med.* 186, 601-612.

Iwasaki, H., Ota, N., Nakajima, T., Shinohara, Y., Kodaira, M., Kajita, M., and Emi, M. (2001). Five novel single-nucleotide polymorphisms of human interferon gamma identified by sequencing the entire gene. *J. Hum. Genet.* 46, 32-34.

Kotenko, S.V, Gallagher, G., Baurin, V.V., Lewis-Antes, A., Shen, M., Shah, N.K., Langer, J.A., Sheikh, F., Dickensheets, H., and Donnelly, R.P. (2003). IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat. Immunol.* 4, 69-77.

Lafaille, J.J., Keere, F.V., Hsu, A.L., Baron, J.L., Haas, W., Raine, C.S., and Tonegawa, S. (1997). Myelin basic protein- specific T helper 2 (Th2) cells cause experimental autoimmune encephalomyelitis in immuno-deficient hosts rather than protect them from the disease. *J. Exp. Med.* 186, 307-312.

Nakao, F., Ihara, K., Kusuhara, K., Sasaki, Y., Kinukawa, N., Takabayashi, A., Nishima, S., and Hara, T. (2001). Association of IFN-gamma and IFN regulatory factor 1 polymorphisms with childhood atopic asthma. *J. Allergy Clin. Immunol.* 107, 499-504.

O'Garra, A. (1998). Cytokines induce the development of functionally heterogeneous T helper cell subsets. *Immunity* 8, 275-283.

Onishi, M., Nosaka, T., and Kitamura, T. (1998). Cytokine receptors: structures and signal transduction. *Int. Rev. Immunol.* 16, 617-634.

O'shea, J.J., Ma, A., and Lipsky, P. (2002). Cytokines and autoimmunity. *Nat. Rev. Immunol.* 2, 37-45.

Sheppard, P., Kindsvogel, W., Xu, W., Henderson, K., Schlutsmeyer, S., Whitmore, T.E., Kuestner, R., Garrigues, U., Birks, C., Roraback, J., Ostrander, C., Dong, D., Shin, J., Presnell, S., Fox, B., Haldeman, B., Cooper, E., Taft, D., Gilber,t T., Grant, F.J., Tackett, M., Krivan, W., McKnight, G., Clegg, C., Foster, D., and Klucher, K.M. (2003). IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat. Immunol.* 4, 63-68.