

ORIGINAL PAPER

A polymorphism of *MS4A2* (–109T > C) encoding the β -chain of the high-affinity immunoglobulin E receptor (Fc ϵ R1 β) is associated with a susceptibility to aspirin-intolerant asthma

S. –H. Kim*, J. –S. Bae*, J. W. Holloway†, J. –T. Lee‡, C. –H. Suh*, D. –H. Nahm* and H. –S. Park*

*Department of Allergy and Rheumatology, Ajou University School of Medicine, Suwon, Korea, †Human Genetics Division, School of Medicine, University of Southampton, Southampton, UK and ‡College of information and communication, Ajou University, Suwon, Korea

Clinical and Experimental Allergy

Summary

Background and objective The *MS4A2* gene, the β chain of the high-affinity receptor for immunoglobulin (Ig)E, has previously been linked to atopy and asthma. The β -chain of Fc ϵ R1 enhances receptor maturation and signal transduction capacity, leading to the release of proinflammatory mediators and cytokines that can exacerbate the symptom of asthma. This study was performed to evaluate whether two genetic polymorphisms of the Fc ϵ R1 β gene (Fc ϵ R1 β –109T > C and Fc ϵ R1 β E237G) are associated with aspirin-intolerant asthma (AIA). **Methods** The *MS4A2* gene polymorphisms (Fc ϵ R1 β –109T > C and Fc ϵ R1 β E237G) were determined by SNP-IT™ assays in patients with AIA (*N* = 164), aspirin-tolerant asthma (ATA, *N* = 144) and normal controls (NC, *N* = 264) recruited from a Korean population.

Results The genotype frequencies of Fc ϵ R1 β –109T > C and E237G polymorphisms were not significantly associated with the pathogenesis of AIA. However, Fc ϵ R1 β –109T > C polymorphism was significantly associated with the presence of specific IgE to *Staphylococcal enterotoxin B* (SEB); the number of subjects carrying both homozygous TT genotype of Fc ϵ R1 β –109T > C and specific IgE to SEB was significantly higher in the AIA group when compared with the other control groups (*P* = 0.01, odds ratio (OR) = 7.723, 95% confidence interval (CI) = 1.327–39.860 for AIA vs. ATA; *P* = 0.02, OR = 6.364, 95% CI = 1.149–35.229 for AIA vs. NC). In addition, luciferase reporter assays also showed that the Fc ϵ R1 β –109T allele was associated with higher promoter activity of *MS4A2* in both RBL-2H3 and A549 cell lines. **Conclusion** Fc ϵ R1 β –109T > C polymorphism may increase expression of *MS4A2* by mast cells, leading to enhanced release of proinflammatory mediators in the asthmatic airway, contributing to increased susceptibility to AIA.

Keywords aspirin-intolerant asthma, Fc ϵ R1 β polymorphism, *MS4A2* gene, Staphylococcal superantigen

Submitted 12 May 2005; revised 29 August 2005; accepted 25 October 2005

Correspondence:

Hae-Sim Park, Department of Allergy and Rheumatology, Ajou University School of Medicine, Paldalgu Wonchondong San-5, Suwon 442-721, Korea.
E-mail: hspark@ajou.ac.kr

Introduction

It is widely recognized that ingestion of aspirin (acetylsalicylic acid (ASA)) can induce bronchoconstriction in patients with ASA-intolerant asthma (AIA) by triggering cysteinyl-leukotriene (Cys-LT) overproduction [1], but the pathogenic mechanism of AIA has not been completely elucidated.

The *MS4A2* gene located on chromosome 11q13 is known to be linked to atopy and asthma [2–4]. The β -chain of Fc ϵ R1 is involved in enhancing receptor

maturation, leading to an increase of Fc ϵ R1 surface expression and signal transduction capacity within cells [5, 6]. Ligation of allergen to immunoglobulin (Ig)E-occupied Fc ϵ R1 on mast cells triggers the release of mediators such as prostaglandins, leukotrienes, proinflammatory cytokines such as IL-4, IL-5, IL-13, TNF- α and chemokines including IL-8, monocyte chemotactic protein 1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), MIP-1 β [6, 7]. These mediators lead to mucus production, inflammatory cell infiltration and smooth muscle constriction, the main pathophysiological features

of asthma. Mast cells are also known to be initiators of both the early and the late phases of bronchial hypersensitivity [8]. Considering that mast cell activation by IgE binding via a high-affinity receptor can increase the concentration of Cys-LTs in the asthmatic airway, we speculated that a genetic abnormality of the *MS4A2* gene may participate in the development of AIA. It is known that genetic polymorphisms of *MS4A2* gene are associated with asthma [9], allergy [10], bronchial hyper-responsiveness [11] and atopic dermatitis [12]. We hypothesized that the polymorphism of the *MS4A2* gene encoding FcεR1β may play a role in the development of AIA.

It is also apparent that a complex interaction between genetic and environmental factors is likely to be important in determining the pathology of AIA. *Staphylococcal* superantigens as environmental factors have been reported to mediate degranulation of mast cells in certain conditions [13–16]. We have therefore investigated whether two previously identified polymorphisms of the *MS4A2* gene (FcεR1β-109T > C and FcεR1β E237G) are associated with susceptibility to AIA, either alone, or through interaction with the environmental exposure of *Staphylococcal* superantigens.

Materials and methods

Subjects

Three study subject groups (164 patients with AIA, 144 patients with aspirin-tolerant asthma (ATA) and 264 normal controls (NC)) were enrolled from Ajou University Hospital in Suwon, Korea. The diagnosis of AIA was based on a positive response to the lysine-ASA bronchoprovocation test, which was performed on all the asthmatic subjects according to the previously described method [17]. Change of forced expiratory volume in 1 s (FEV₁) was followed up to 7 h after the last dose of aspirin challenge. ATA was defined as negative responders on the lysine-

ASA bronchoprovocation test. All the subjects classified as NC had never had asthma or other allergic diseases. Atopy was defined as one or more positive reactions on skin prick test, using 12 common aeroallergens (Bencard, Brentford, UK) with histamine and saline controls. Total IgE and specific IgE to *Staphylococcal* superantigens including *Staphylococcal enterotoxin A* (SEA), *Staphylococcal enterotoxin B* (SEB) and *toxic shock syndrome toxin 1* (TSST-1) were measured using the UniCAP system (Pharmacia Diagnostics, Valinge, Sweden) according to the manufacturer's instructions. The study protocol was approved by the institutional review board of Ajou University Hospital, Korea, and all the subjects gave their informed consent. The clinical characteristics of the study subjects are summarized in Table 1. There were significant differences in the mean age and the atopic status between the AIA and NC groups ($P < 0.001$, $P < 0.001$, respectively). Between the AIA and ATA groups, there were significant differences in baseline FEV₁ level and the presence of rhinosinusitis ($P = 0.002$ and 0.017 , respectively).

Genotyping

SNP genotyping was performed by SNP-IT™ assays using the SNPstream 25K™ System (Orchid Biosciences, Princeton, NJ, USA). Sequences of amplifying and extension primers for FcεR1β -109T > C and FcεR1β E237G were forward-5'-aaaattatgtctcaggagtctca-3', reverse 5'-at aagtttcttggtgctgattaagatca-3', extension-5'-ttactgtgatgaat agaaaaatt-3' (FcεR1β -109T > C) forward-5'-agaggatcgt gtttatgaagaattaac-3', reverse 5'-gaatcagagtgttctggacacgt -3', extension-5'-cttacagtgttggaagacxcagggg-3' (FcεR1β E237G).

Transfection and luciferase assays

A 331bp fragment (from -229 to +102) of the human FcεR1β gene promoter was prepared by PCR amplification

Table 1. Clinical characteristics of the study subjects

	AIA [†]	ATA [†]	NC [†]	P-value		
	(N = 164)	(N = 144)	(N = 264)	AIA vs. ATA	AIA vs. NC	ATA vs. NC
Age (year)*	43.5 ± 13.4	41.1 ± 14.7	37.2 ± 15.8	0.132	< 0.001	0.015
Sex (male/total)	67/164 (40.9%)	69/144 (47.9%)	114/264 (43.2%)	0.213	0.636	0.358
Atopy (presence/total)	80/151 (53.0%)	84/142 (59.2%)	33/228 (14.5%)	0.287	< 0.001	< 0.001
FEV ₁ (%)*	78.3 ± 27.2	87.2 ± 21.6	NA	0.002	NA	NA
PC ₂₀ methacholine (mg/mL)*	10.5 ± 33.8	12.9 ± 19.8	NA	0.520	NA	NA
Log [serum total IgE, IU/mL] *	2.2 ± 0.6	2.2 ± 0.7	NA	0.882	NA	NA
Rhinosinusitis (presence/total)	104/128 (81.3%)	96/140 (68.6%)	NA	0.017	NA	NA

*This value was presented as means ± SD, NA, not applicable. Values in bold indicate significant P value.

[†]AIA, ASA-intolerant asthma; NC; normal controls; ATA, ASA-tolerant asthma; ASA, acetylsalicylic acid; FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E.

[§]SEA, *Staphylococcal enterotoxin A*; SEB, *Staphylococcal enterotoxin B*; TSST-1, toxic shock syndrome toxin1.

of either –109T homozygote or –109C homozygote human genomic DNA as a template, using a pair of primers (forward primer, 5'-CAAGGTACCAACTCCTACTAAAATGTCTC-3'; the bold character represents the *KpnI* site, reverse primer, 5'-CTGTGTCCATggTTTCATTAACCGA-3'; the bold character represents the *NcoI* site, and small letter gg is substituted for tt to create an *NcoI* site and **CAT** represents the translational start site). To introduce an *NcoI* site at the translation initiation site, nucleotide replacement was performed using an *NcoI* mutagenic primer [18]. Each of the PCR products was separately subcloned into a *KpnI*-*NcoI* site of the pGL3-Basic luciferase reporter vector (Promega, Madison, WI, USA).

RBL-2H3 (rat basophilic cell line, No.22256, KCLB, Seoul, Korea) were cultured in DMEM (Invitrogen, Carlsbad, CA, USA), and A549 (bronchial epithelial carcinoma cell line, No.10185 KCLB) cells were cultured in RPMI 1640 (Invitrogen) at 37 °C in a 5% CO₂ incubator. All media were supplemented with 10% fetal bovine serum (FBS), 1 mM sodium pyruvate, 100 U/mL of penicillin G and 100 µg/mL streptomycin (Invitrogen). RBL-2H3 and A549 cells were transfected by using lipofectamine (Invitrogen) according to the manufacturer's instructions. Briefly, the day before the transfection, 1×10^5 cells for RBL-2H3 and 8×10^4 cells for A549 per well of a 12-well plate in 1 mL of the medium with 10% FBS were seeded. One microgram of reporter plasmid DNA and 5 µL of lipofectamine were added to 100 µL medium without FBS and antibiotics, mixed gently and incubated at room temperature for 30 min and then added to cells that had attained 40–60% confluence in 12-well plates containing 0.4 mL of medium without FBS and antibiotics. The pGL3-Control (Promega) and the promoter-less pGL3-Basic vectors were used as the positive and negative controls, respectively. Transfection efficiency was determined by measuring β-galactosidase activity assay after co-transfection of both constructors, reporter construct and pSV-β-galactosidase control vector, into the cell line. After

incubation for 5 h, the medium was added with 800 mL of fresh medium with 20% FBS, and the cells were incubated a further 24 h for RBL-2H3 and 48 h for A549. Cells were then lysated with 100 µL of reporter lysis buffer (Promega) per well. Twenty microlitres from 100 µL of the cell lysate were assayed for luciferase activity using a luciferase assay kit (Promega) and a luminometer TD20/20 (Turner BioSystems, Sunnyvale, CA, USA).

Statistical analysis

Significant departures of genotype frequency from the Hardy-Weinberg equilibrium (HWE) at each SNP were tested by χ^2 analysis. Differences in genotype frequency between case and control were tested by the χ^2 test and calculation of odds ratio (OR) with 95% confidence interval (CI). Logistic regression models were used for analyses of SNPs and haplotypes controlling age and sex as covariates with three alternative models (co-dominant, dominant and recessive models). Haplotypes of FcεR1β gene were analysed using Haploview v2.0 based on the EM algorithm [19]. Linkage disequilibrium between loci was measured using the absolute value of Lewontin's $|D'|$ [20]. Differences in the mean value of the phenotypic characteristics within AIA patients were compared using the ANOVA test and the *t*-test. Statistical analyses were undertaken using SPSS v11 (SPSS Inc., Chicago, IL, USA). *P*-values of < 0.05 were considered to be significant.

Results

Allele and genotype frequencies of the MS4A2 gene

We performed a genetic association study of two genetic polymorphisms of MS4A2 (FcεR1β 109T > C, FcεR1β E237G) in three groups of study subjects classified as AIA, ATA and NC. Allele and genotype frequencies of two

Table 2. Genotype and allele frequencies of FcεR1

Loci	Genotype	AIA [†] (N = 164)	ATA [†] (N = 144)	NC [†] (N = 264)	P-value		
					AIA vs. ATA	AIA vs. NC	ATA vs. NC
–109T > C	TT	79 (48.8%)	67 (47.9%)	113 (42.8%)	0.83	0.24	0.32
	CT	74 (45.7%)	65 (46.4%)	128 (48.5%)	0.99	0.32	0.39
	CC	9 (5.6%)	8 (5.7%)	23 (8.7%)	0.80	0.36	0.44
	q.	0.284	0.289	0.330	0.84	0.27	0.35
E237G	AA	125 (76.2%)	110 (76.9%)	177 (67.0%)	0.82	0.19	0.09
	AG	34 (20.7%)	30 (21.0%)	81 (30.7%)	0.46	0.52	0.93
	GG	5 (3.0%)	3 (2.1%)	6 (2.3%)	1.00	0.09	0.06
	q.	0.134	0.126	0.176	0.81	0.19	0.09

Each *P*-value was calculated with co-dominant, dominant, and recessive models. Logistic regression analysis was applied to control for age and sex as covariables. q., minor allele frequency.

[†]AIA, ASA-intolerant asthma; NC, normal controls; ATA, ASA-tolerant asthma; ASA, acetylsalicylic acid.

Table 3. Comparison of the clinical characteristics according to the genotype of FcεR1β in ASA-intolerant asthma (AIA) patients

	- 109 T > C			E237G		
	TT	CT or CC	P-value	AA	AG or GG	P-value
Sex (male/total)	30/79 (38.0%)	35/83 (42.2%)	0.59	51/125 (40.8%)	16/39 (41.0%)	0.98
Atopy (presence/total)	42/73 (57.5%)	37/76 (48.7%)	0.28	60/115 (52.2%)	20/36 (55.6%)	0.72
Asthma duration (year)*	7.2 ± 6.1	6.1 ± 5.7	0.30	6.8 ± 5.8	6.3 ± 6.4	0.71
FEV ₁ (%)*	72.3 ± 26.8	80.8 ± 27.7	0.21	77.0 ± 27.1	82.4 ± 25.6	0.29
PC ₂₀ methacholine (mg/mL)*	6.8 ± 16.4	12.3 ± 42.7	0.39	12.5 ± 38.1	4.0 ± 10.9	0.27
Log [serum total IgE, IU/mL]*	2.3 ± 0.6	2.1 ± 0.5	0.09	2.2 ± 0.6	2.2 ± 0.6	0.69
Rhinosinusitis (presence/total)	50/159 (84.7%)	53/67 (79.1%)	0.41	81/98 (82.7%)	23/30 (76.7%)	0.46
Specific IgE to SEA [†] (positive/total)	7/21 (33.3%)	2/23 (8.7%)	0.04	8/28 (28.6%)	1/15 (6.7%)	0.09
Specific IgE to SEB [†] (positive/total)	10/21 (47.6%)	4/23 (17.4%)	0.03	11/28 (39.3%)	3/15 (20.0%)	0.20
Specific IgE to TSST-1 [†] (positive/total)	5/21 (23.8%)	4/23 (17.4%)	0.60	7/28 (25.0%)	2/15 (13.3%)	0.37

*This value was presented as means ± SD. Values in bold indicate significant P value.

[†]SEA; *Staphylococcal enterotoxin A*, SEB; *Staphylococcal enterotoxin B*, TSST-1; toxic shock syndrome toxin1; ASA, acetylsalicylic acid; FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E; TSST-1, toxic shock syndrome toxin1.

Table 4. Synergistic effects of FcεR1β -109 and specific IgE to SEB on AIA development

- 109T > C	Specific IgE to SEB				AIA vs. ATA		AIA vs. NC		ATA vs. NC	
		AIA	ATA	NC	P-value	OR	P-value	OR	P-value	OR
TT	Positive	10 (47.6%)	2 (11.1%)	2 (12.5%)	0.01	7.273	0.02	6.364	0.9	0.875
	Negative	11 (52.4%)	16 (88.9%)	14 (87.5%)						
		N = 21	N = 18	N = 16	95% CI = 1.327~39.860		95% CI = 1.149~35.229			
CT or CC	Positive	4 (17.4%)	2 (13.3%)	1 (4.2%)	0.74	1.368	0.14	4.842	0.3	3.538
	Negative	19 (82.6%)	13 (86.7%)	23 (95.8%)						
		N = 23	N = 15	N = 24						

SEB, *Staphylococcal enterotoxin B*; AIA, aspirin-intolerant asthma; NC, normal controls; ATA, aspirin-tolerant asthma; OR, odds ratio; CI, confidence interval; IgE, immunoglobulin E.

polymorphisms of FcεR1β gene are shown in Table 2. No significant differences in allele and genotype frequencies of the *MS4A2* gene polymorphisms (FcεR1β -109T > C, FcεR1β E237G) were observed among the three study groups. These two polymorphisms in the FcεR1β gene were in linkage disequilibrium ($|D'| = 0.95$) and three common haplotypes, ht1 [TA], ht2 [CG] and ht3 [CA], were constructed utilizing the EM algorithm. However, there was no significant differences among the three groups in the observed haplotype frequencies ($P > 0.05$, respectively, data not shown).

Association of FcεR1β -109T > C with specific immunoglobulin E to *Staphylococcal enterotoxin B*

Asthma-associated quantitative phenotypes such as atopy, serum total IgE level, initial baseline FEV₁ and PC₂₀ methacholine values were evaluated for any association with two polymorphisms of *MS4A2* gene (Table 3). Within the AIA group, no significant association of quantitative traits with either polymorphism was noted. However, there was a significant association of FcεR1β -109T > C

polymorphism with the prevalence of serum-specific IgE to *Staphylococcal* superantigens; AIA patients carrying the homozygous TT genotype of FcεR1β -109T > C had a significantly higher prevalence of specific IgE to SEA and SEB than AIA patients carrying homozygous CC or heterozygous CT genotypes ($P = 0.04$, OR = 5.25, 95% CI = 0.949–29.050 for SEA, $P = 0.03$, OR = 4.32, 95% CI = 1.090–17.112 for SEB). This association of *Staphylococcal* superantigens with FcεR1β -109T > C polymorphism was not replicated in ATA or NC groups. We further analysed a possible gene–environment interaction between FcεR1β -109T > C polymorphism and *Staphylococcal* superantigens among the three groups. This analysis revealed a significant synergistic effect of FcεR1β -109T > C polymorphism and the prevalence of serum-specific IgE to SEB on AIA development; the number of subjects carrying both homozygous TT genotype of FcεR1β -109T > C and specific IgE to SEB was significantly higher in the AIA group than in the other control groups ($P = 0.01$, OR = 7.723, 95% CI = 1.327–39.860 for AIA vs. ATA; $P = 0.02$, OR = 6.364, 95% CI = 1.149–35.229 for AIA vs. NC, Table 4).

Modulation of the promoter activity of *MS4A2* gene by –109T > C polymorphism

To examine whether FcεR1β –109T > C polymorphism is associated with altered promoter activity, a construct composed of promoter sequence and luciferase reporter gene was transfected into the RBL-2H3 cell line. This cell line represents an appropriate mast cell model. Reporter activities were compared between constructs containing either FcεR1β –109T or FcεR1β –109C in the FcεR1β gene promoter region (Fig. 1a). Luciferase activity was significantly enhanced in the construct containing FcεR1β –109T when compared with the –109C-containing construct ($P=0.01$). Additional transfection experiments were performed in the A549 bronchial epithelial cell line in which significantly higher luciferase activity was also noted for the FcεR1β –109T construct in comparison with the FcεR1β –109C construct ($P=0.004$, Fig. 1b).

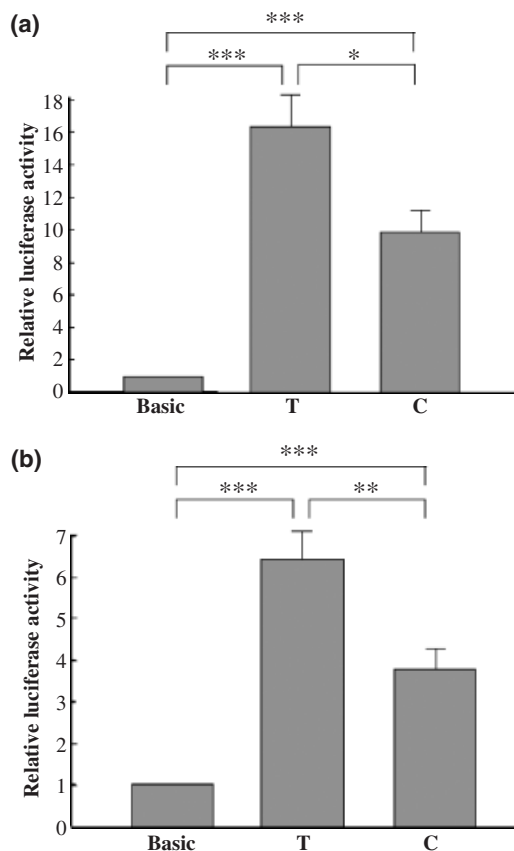


Fig. 1. Effect of –109T > C polymorphism on the transcription activity of human FcεR1 α -chain promoter. Data are the mean values of independent experiments, plus or minus the SEM. (a) Transfection of RBL-2H3 cells. Luciferase activity assay was performed in three independent experiments (in total, $n=9$). (b) Transfection of A549 cell ($n=9$). Relative luciferase activity is represented as the ratio of the activity to the luciferase activity in the cells transfected with the empty control vector pGL3-Basic. * $P=0.011$; ** $P=0.004$; *** $P<0.001$, as determined by a paired t -test.

Discussion

As mast cell activation in the airway results in the release of inflammatory mediators such as Cys-LTs and prostaglandin D₂, known to be important in the pathogenesis of AIA, we hypothesized that the *MS4A2* gene encoding FcεR1β may contribute to immediate hypersensitivity to ASA in the asthmatic airway. We therefore assessed the frequency of polymorphisms of *MS4A2* gene in patients with AIA compared with ATA and normal healthy controls. It has been shown that the β chain of the high-affinity receptor for IgE is an amplifier for cell surface expression in association with the α chain and an enhancer for signal transduction via an immunoreceptor tyrosine activation motif (ITAM) of the γ chain of FcεR1 [5, 21]. Furthermore, genetic polymorphisms of *MS4A2* gene have been reported to be associated with asthma [9], allergy [10], bronchial hyper-responsiveness (BHR) [11] and atopic dermatitis [12]. In particular, FcεR1β E237G polymorphism, which lies adjacent to the ITAM of FcεR1β, was associated with a higher prevalence of atopy and BHR [22], total and specific IgE level [23] and histamine release ability in basophils [24]. FcεR1β –109T > C polymorphism has previously been shown to be associated with total serum IgE levels in a Japanese population [25, 26].

In this study, there was no significant association of either *MS4A2* gene polymorphism with susceptibility to AIA. However, FcεR1β –109T > C polymorphism was significantly associated with the presence of specific IgE to SEB. Previous studies demonstrated the association of both FcεR1β –109T > C and FcεR1β E237G polymorphisms with serum total IgE level [23, 25, 26]; however, we were unable to replicate these observations in our study groups. In contrast, AIA patients carrying the homozygous TT genotype of FcεR1β –109T > C showed a tendency towards a higher serum total IgE level than those with the homozygous CC genotype or the heterozygous CT genotype. These findings may be due to differences in study populations between studies, with this study focused on an AIA.

Despite the postulated pathophysiological role for the FcεR1β –109T > C polymorphism in asthma, the functional role of this polymorphism is still unclear. Utilizing a reporter–promoter assay, we demonstrated that the FcεR1β –109T > C polymorphism had a direct effect on basal transcription of the *MS4A2* gene. Constructs containing FcεR1β –109T showed significantly higher promoter activity than the construct with FcεR1β –109C in the rat basophilic cell line, RBL-2H3. These effects were also replicated in the A549 cell line, suggesting that the FcεR1β –109T allele may increase expression of the *MS4A2* gene. To investigate whether the genetic variants create a transcription factor binding site, sequences were submitted to the 'Signal Scan' online program (www.bimas.cit.nih.gov/molbio/signal) and compared with

mammalian transcription factor binding sequences in the transcription factors (TRANSFAC) database. There was no transcription factor binding site matching the FcεR1β – 109T > C polymorphism. Although a transcription factor that can bind to positions – 109T > C was not identified, it may be possible that transversion of the C allele to the T allele at the FcεR1β – 109 polymorphic region may have created an unknown transcription factor binding sequence, resulting in an increased expression of *MS4A2* by mast cells. Recently, no significant difference in promoter activity between FcεR1β – 109T and FcεR1β – 109C was reported in HML/SE cells (a megakaryocyte cell line) [26]. Differences between these studies may relate to the use of different cell lines. Further functional analyses of the effect of FcεR1β – 109T > C polymorphism in other cell lines to verify the functional implications of the FcεR1β – 109T > C polymorphism alone, and in conjunction with other promoter polymorphisms [26], are needed.

It has been reported that superantigens such as *Staphylococcal* enterotoxins may stimulate mast cell activation, leading to the release of proinflammatory mediators and Th2 cytokines [27, 28]. These mediators have an effect on exacerbation of asthma-related pathophysiology such as mucus secretion, bronchoconstriction and airway hyper-responsiveness [29, 30]. We have previously reported that specific IgE levels to SEA and SEB in the nasal polyp tissue from AIA subjects are remarkably higher than in those of ATA subjects [31], suggesting that these specific IgE to *Staphylococcal* superantigens could be involved in the pathogenesis of AIA. In this study, the prevalence of serum-specific IgE to SEA and SEB was significantly higher in patients with the homozygous TT genotype of FcεR1β – 109T > C, and the presence of the FcεR1β – 109T allele and specific IgE level to SEB, but not SEA, synergistically increased susceptibility to AIA ($P=0.01$, OR = 7.723, 95% CI = 1.327–39.860 for AIA vs. ATA; $P=0.02$, OR = 6.364, 95% CI = 1.149–35.229 for AIA vs. NC). These findings suggest that specific IgE to *Staphylococcal* superantigens might contribute to the airway inflammation in AIA. One of the possible mechanisms for this synergistic effect of FcεR1β – 109T > C polymorphism and specific IgE to SEB on the susceptibility to AIA is that the interaction of SEB with IgE bound to its high-affinity receptor, FcεR1, on the mast cell surface results in mast cell activation that might be augmented by increased surface expression of FcεR1β in patients carrying the FcεR1β – 109T allele.

In conclusion, the FcεR1β – 109T allele may increase expression of FcεR1 on mast cells and enhance the release of inflammatory mediators and T helper type 2 cytokines, contributing to increased susceptibility to AIA.

Source of funding: This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea. (03-PJ10-PG13-GD01-0002).

References

- 1 Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis, and management. *J Allergy Clin Immunol* 2003; 111:913–21.
- 2 Sandford AJ, Shirakawa T, Moffatt MF *et al*. Localisation of atopy and beta subunit of high-affinity IgE receptor (FcεRI) on chromosome 11q. *Lancet* 1993; 341:332–4.
- 3 Cookson WO, Sharp PA, Faux JA, Hopkin JM. Linkage between immunoglobulin E responses underlying asthma and rhinitis and chromosome 11q. *Lancet* 1989; 1:1292–5.
- 4 Daniels SE, Bhattacharya S, James A *et al*. A genome-wide search for quantitative trait loci underlying asthma. *Nature* 1996; 383:247–50.
- 5 Donnadieu E, Jouvin MH, Kinet JP. A second amplifier function for the allergy-associated Fc (epsilon) RI-beta subunit. *Immunity* 2000; 12:515–23.
- 6 von Bubnoff D, Novak N, Kraft S, Bieber T. The central role of FcεRI in allergy. *Clin Exp Dermatol* 2003; 28:184–7.
- 7 Costa JJ, Weller PF, Galli SJ. The cells of the allergic response: mast cells, basophils, and eosinophils. *JAMA* 1997; 278:1815–22.
- 8 Toru H, Pawankar R, Ra C, Yata J, Nakahata T. Human mast cells produce IL-13 by high-affinity IgE receptor cross-linking: enhanced IL-13 production by IL-4-primed human mast cells. *J Allergy Clin Immunol* 1998; 102:491–502.
- 9 Shirakawa T, Mao XQ, Sasaki S *et al*. Association between atopic asthma and a coding variant of FcεRI in a Japanese population. *Hum Mol Genet* 1996; 5:1129–30.
- 10 Hill MR, James AL, Faux JA *et al*. FcεRI-β polymorphism and risk of atopy in a general population sample. *Br Med J* 1995; 311:776–9.
- 11 van Herwerden L, Harrap SB, Wong ZY *et al*. Linkage of high-affinity IgE receptor gene with bronchial hyperreactivity, even in absence of atopy. *Lancet* 1995; 346:1262–5.
- 12 Cox HE, Moffatt MF, Faux JA *et al*. Association of atopic dermatitis to the b subunit of the high affinity immunoglobulin E receptor. *Br J Dermatol* 1998; 138:182–7.
- 13 Komisar J, Rivera J, Vega A, Tseng J. Effects of staphylococcal enterotoxin B on rodent mast cells. *Infect Immun* 1992; 60:2969–75.
- 14 Alber G, Scheuber PH, Reck B, Sailer-Kramer B, Hartmann A, Hammer DK. Role of substance P in immediate-type skin reactions induced by staphylococcal enterotoxin B in unsensitized monkeys. *J Allergy Clin Immunol* 1989; 84:880–5.
- 15 Scheuber PH, Denzlinger C, Wilker D, Beck G, Keppler D, Hammer DK. Staphylococcal enterotoxin B as a nonimmunological mast cell stimulus in primates: the role of endogenous cysteinyl leukotrienes. *Int Arch Allergy Appl Immunol* 1987; 82:289–91.
- 16 Ackermann L, Pelkonen J, Harvima IT. Staphylococcal enterotoxin B inhibits the production of interleukin-4 in a human mast-cell line HMC-1. *Immunol* 1998; 94:247–52.
- 17 Park HS. Early and late onset asthmatic responses following lysine-aspirin inhalation in aspirin-sensitive asthmatic patients. *Clin Exp Allergy* 1995; 25:38–40.
- 18 Akizawa Y, Nishiyama C, Hasegawa M *et al*. Regulation of human FcεRI beta chain gene expression by Oct-1. *Int Immunol* 2003; 15:549–56.
- 19 Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 2005; 21:263–5.

- 20 Hedrick PW. Gametic disequilibrium measures: proceed with caution. *Genetics* 1987; **117**:331–41.
- 21 Dombrowicz D, Lin S, Flamand V, Brini AT, Koller BH, Kinet JP. Allergy-associated FcRbeta is a molecular amplifier of IgE- and IgG-mediated in vivo responses. *Immunity* 1998; **8**:517–29.
- 22 Hill MR, Cookson WO. A new variant of the b subunit of the high-affinity receptor for immunoglobulin E (FcεRI-b E237G): associations with measures of atopy and bronchial hyperresponsiveness. *Hum Mol Genet* 1996; **5**:959–62.
- 23 Young RP, Sharp PA, Lynch JR *et al.* Confirmation of genetic linkage between atopic IgE responses and chromosome 11q13. *J Med Genet* 1992; **29**:236–8.
- 24 Kim YK, Oh SY, Oh HB *et al.* Coding single nucleotide polymorphism in the high-affinity immunoglobulin E receptor b chain (FcεRI-b) gene is associated with immunoglobulin E receptor-mediated histamine release from basophils. *Clin Exp Allergy* 2002; **32**:751–5.
- 25 Hizawa N, Yamaguchi E, Jinushi E, Kawakami Y. A common FCER1B gene promoter polymorphism influences total serum IgE levels in a Japanese population. *Am J Respir Crit Care Med* 2000; **161**:906–9.
- 26 Nishiyama C, Akizawa Y, Nishiyama M *et al.* Polymorphisms in the Fc epsilon RI beta promoter region affecting transcription activity: a possible promoter-dependent mechanism for association between Fc epsilon RI beta and atopy. *J Immunol* 2004; **173**:6458–64.
- 27 Turner H, Kinet JP. Signaling through the high-affinity IgE receptor FcεRI. *Nature* 1999; **402**:24–30.
- 28 Mekori YA, Metcalfe DD. Mast cells in innate immunity. *Immunol Rev* 2000; **173**:131–40.
- 29 Eum SY, Maghni K, Hamid Q, Campbell H, Eidelman DH, Martin JG. Involvement of the cysteinyl-leukotrienes in allergen-induced airway eosinophilia and hyperresponsiveness in the mouse. *Am J Respir Cell Mol Biol* 2003; **28**:25–32.
- 30 Parameswaran K, Cox G, Radford K, Janssen LJ, Sehmi R, O'Byrne PM. Cysteinyl leukotrienes promote human airway smooth muscle migration. *Am J Respir Crit Care Med* 2002; **166**:738–42.
- 31 Suh YJ, Yoon SH, Sampson AP *et al.* Specific immunoglobulin E for staphylococcal enterotoxins in nasal polyps from patients with aspirin-intolerant asthma. *Clin Exp Allergy* 2004; **34**: 1270–5.