ORIGINAL ARTICLE

Association Between Polymorphisms in *IL17F* and Male Asthma in a Chinese Population

F Qian,[1*] Q Zhang,[2*] L Zhou,[3] G Ma,[1] G Jin,[4] Q Huang,[5] K Yin[3]

[1]Department of Respiratory Medicine, Affiliated Hospital, Jiangsu University, Zhenjiang, Jiangsu, China
[2]Department of Respiratory Medicine, Affiliated Changzhou No.2 People's Hospital, Nanjing Medical University, Changzhou, China
[3]Department of Respiratory Medicine, First Affiliated Hospital, Nanjing Medical University, Nanjing, China
[4]Department of Epidemiology and Biostatistics, Cancer Research Center, Nanjing Medical University, Nanjing, China
[5]Department of Otolaryngology, Affiliated Hospital, Jiangsu University, Zhenjiang, Jiangsu, China
*These authors contributed equally to the article.

Abstract

Background and Objectives: Interleukin (IL) 17F is a marker of type 17 helper T cells and has a proinflammatory role in asthma. The aim of the present study was to assess the possible association between asthma and polymorphisms in the *IL17F* gene in a Chinese population.
Methods: A total of 318 asthmatic patients and 352 nonasthmatic controls were recruited. Two single-nucleotide polymorphisms in *IL17F* (rs763780 and rs13209590) were detected using GenomeLab SNPstream. Logistic regression methods were used to analyze data.
Results: A significantly lower frequency of the C allele in rs763780 was observed in the control group (*P*=.0148). The rs763780 TC heterozygote was associated with an increased risk of asthma, and a similar trend was observed assuming a codominant genotype effect (adjusted OR, 1.58; 95% CI, 1.06-2.36; *P*=.0148; adjusted OR, 1.64; 95% CI, 1.10-2.45; *P*=.0217). Furthermore, a novel finding of the present study was that this association was exclusive to males (adjusted OR, 1.79; 95% CI, 1.06-3.05; *P*=.0308) and patients with higher immunoglobulin E levels (≥ 1.85 IU/mL) (adjusted OR, 1.88; 95% CI, 1.10-3.22; *P*=.0213). We also found that the haplotype with minor alleles for rs763780 was associated with an increased risk of asthma (adjusted OR, 1.62; 95% CI, 1.11-2.35; *P*=.0115).
Conclusion: Our findings indicated that polymorphisms might play a role in susceptibility to asthma.

Key words: Asthma. IgE. Interleukin 17F. Single-nucleotide polymorphism.

Resumen

Introducción y objetivos: La interleucina (IL) 17F es un marcador de las células T 17 cooperadoras y desempeña un papel proinflamatorio en el asma bronquial. La finalidad de este estudio ha sido el determinar la posible asociación entre el padecer asma y diferentes polimorfismos en el gen de IL17F en una población china.
Métodos: Se seleccionó a un total de 318 pacientes asmáticos y a 352 controles sin asma bronquial. Se estudiaron dos polimorfismos de un único nucleótido (SNIP) en IL17F (rs763780 y rs13209590) mediante GenomeLab SNPstream. Los resultados se analizaron utilizando métodos de regresión logística.
Resultados: En el grupo control se observó una frecuencia significativamente más baja del alelo C en rs763780 (*P*=.0148). El heterocigoto TC de rs763780 se asoció a un riesgo superior de padecer asma y una tendencia similar se observó asumiendo un efecto codominante del genotipo (OR ajustado, 1.58; IC del 95%, 1.06-2.36; P=.0148; OR ajustado, 1.64; IC del 95%, 1.10-2.45; *P*=.0217). Por otro lado, fue un hallazgo el descubrir que en este estudio, esta asociación se dio exclusivamente en los varones (OR ajustado, 1.79; IC del 95%, 1.06-3.05; *P* = .0308) y en los pacientes con niveles más elevados de inmunoglobulina E (log10 IgE ≥ 1.85 IU/mL, OR ajustado, 1.88; IC del 95%, 1.10-3.22; *P*=.0213). Finalmente, se encontró que el haplotipo con los alelos menos comunes para rs763780 se asoció a un mayor riesgo de asma (OR ajustado, 1.62; IC del 95%, 1.11-2.35; *P*=.0115).
Conclusión: Nuestros hallazgos indican que los polimorfismos pueden desempeñar un papel en la susceptibilidad a desarrollar asma bronquial.

Palabras clave: Asma. IgE. Interleucina 17F. Polimorfismo de un único nucleótido.

Introduction

Asthma is one of the most common chronic inflammatory respiratory disorders and is characterized by airway eosinophilia and elevated immunoglobulin (Ig) E levels. Aberrant T helper (T_H) 2 cells are thought to produce a biased immune response in the development of asthma [1], and T_H2-mediated immunity is important in some asthma endotypes. However, the current T_H2-based inflammation model does not account for the substantial clinical and molecular heterogeneity documented in human asthma [2]. T_H17, a new subset of T_H cells, is characterized by the production of cytokines from the interleukin (IL) 17 family, namely, IL-17A and IL-17F [3,4]. Increasing evidence has shown that T_H17 cells can also participate in the pathogenesis of allergic diseases [5,6], and a major role has been shown for these cells in asthma and in the regulation of feedback for polarization towards distinct T-cell subsets [4,7]. T_H17 cells are not only proinflammatory, but have also been shown to induce corticosteroid resistance in murine models [8].

Interest in IL-17F has been growing because of its significance as a marker of T_H17. It has been well characterized in vitro and in vivo and has a proinflammatory role in asthma. IL-17F is clearly expressed in the airway of asthmatics, and expression is correlated with disease severity [9]. Overexpression of IL-17F in lung epithelium resulted in infiltration of lymphocytes and macrophages and mucus hyperplasia, whereas IL-17F–deficient mice had defective airway neutrophilia in response to an allergen challenge. Moreover, IL-17F–deficient mice also displayed enhanced type 2 cytokine production and eosinophil function in an asthma model [10]. Hyperresponsiveness to corticosteroids in patients with severe asthma may also be associated with the presence of IL-17F [11]. Thus, IL-17F could play a key role in airway inflammation, with important implications for the therapy of patients with asthma.

Epidemiological studies have demonstrated a strong genetic component in the risk of asthma. Our group previously demonstrated that specific polymorphisms have an effect on the risk of asthma in a Chinese population [12]. *IL17F* is located on chromosome 6p12, a genomic region linked to asthma and asthma-related phenotypes [13]. On the basis of experimental findings and gene expression studies, *IL17F* is a good positional candidate gene for asthma. However, current data on the association between *IL17F* polymorphisms and asthma in both Chinese and other populations are inconsistent [14-16]. Therefore, we conducted a case-control study in a Chinese population to evaluate interactions between *IL17F* genotypes/haplotypes and the risk of developing asthma.

Methods

Study Population

The study population comprised 318 asthmatic patients (aged 14 to 75 years) and 352 nonasthmatic controls (aged 16 to 74 years) (Table 1). Participants were unrelated Han Chinese residing in the city of Nanjing and the surrounding regions. The asthmatic cohort was enrolled from the First Affiliated Hospital, Nanjing Medical University. All participants were questioned to obtain clinical and family histories, as well as data on smoking habits, occupation, and medication. Patients underwent a general physical examination, skin prick test (SPT), and spirometry. Blood analysis and extended laboratory examinations were performed. Asthma was diagnosed and severity classified according to the Global Initiative for Asthma guidelines [17]. Patients were subdivided into 4 groups based on clinical features, as follows: stage 1, intermittent; stage 2, mild persistent; stage 3, moderate persistent; and stage 4, severe persistent.

Healthy volunteers (controls) were recruited from patients' spouses and the general population. To be included in the study, controls had to be in good health and match the patients in age, gender, and residential region. In addition, they had to have a negative SPT result and normal levels of plasma total IgE.

Table 1. Demographic Characteristics of Asthmatic Patients and Nonasthmatic Controls[a]

	Cases (n = 318)	Controls (n = 352)	*P*[b]
Age, y	39.80 (14.23)	38.26 (13.31)	NS
Gender, No. (%)			
Female	183 (57.55)	200 (56.82)	NS
Male	135 (42.45)	152 (43.18)	
Smoking, No. (%)			
Nonsmoker	280 (88.05)	292 (82.88)	NS
Smoker	38 (11.95)	60 (17.12)	
Atopy, No. (%)	237 (75.00)	0	–
Eosinophils, $\times 10^9$/L	0.46 (0.71)	0.14 (0.11)	<.0001
Log_{10} IgE, IU/mL	1.82 (0.50)	1.19 (0.60)	<.0001
FEV_1, %	74.11 (23.66)	94.75 (18.07)	<.0001
FEV_1/FVC, %	76.18 (12.78)	88.66 (9.43)	<.0001
Allergic rhinitis, No. (%)			
No	137 (43.08)	0	–
Yes	181 (56.92)	0	–

Abbreviations: FEV_1%, forced expiratory volume in the first second of expiration; FEV_1/FVC, ratio of FEV_1 to forced vital capacity; Ig, immunoglobulin; log_{10}IgE, log_{10}-transformed immunoglobulin E levels; NS, nonsignificant.

[a]Data are presented as means (SD) unless otherwise indicated.

[b]Differences between groups were evaluated using the *t* test or χ^2 test, as appropriate.

The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from all participants.

Assessment of Clinical Data

Cumulative smoking was defined as the number of packs of cigarettes smoked per day multiplied by the number of years smoking (pack-years). Participants who had smoked <5 pack-years were defined as nonsmokers; otherwise, they were considered to be smokers [18]. Atopy was determined by SPT with at least 1 positive result for 13 common aeroallergens, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Felis domesticus, Canis familiaris*, cockroach, pollen, ragweed, mugwort, molds (*Cladosporium* and *Alternaria*), and animal allergens (cat, dog, and horse). Allergic rhinitis was defined as rhinitis appearing at least twice after exposure to a particular allergen and not related to an infection. SPT, total serum IgE levels, and lung function assessments are described in detail elsewhere [19].

Genotyping

DNA was extracted from EDTA-anticoagulated peripheral blood leukocytes using the QIAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer's protocol. As a preliminary study, we selected and genotyped 2 SNPs (Table 2). Genotyping was performed using the GenomeLab SNPstream genotyping platform (Beckman Coulter) and its accompanying SNPstream software suite at the Chinese National Human Genome Center in Shanghai, China. Polymerase chain reaction (PCR) primers and extension probes with tag sequences were designed using the web-based Autoprimer design tool (http://www.autoprimer.com) and synthesized by SBSgene (SBS Genetech Technology). The sequences of the primers used for PCR are shown in Table 2. SNPstream genotyping was performed as described previously [20]. In brief, the SNPs of interest were amplified in a 12-pair multiplex PCR under universal conditions (5 mM MgCl2, 75 μM dNTPs, 0.1 units AmpliTaq Gold [Applied Biosystems] in a final volume of 5 μL). The PCR was run at 94ºC for 1 minute, followed by 34 cycles at 94ºC for 30 seconds, 55ºC for 30 seconds, and 72ºC for 1 minute).

The technician was blind to each sample run, and negative controls were included in each 384-well plate. We duplicated 10% of samples to confirm the concordance and accuracy of genotyping. A sample call rate >99% was observed with 100% matching in the replicates.

Statistical Analysis

Differences in the distributions of the demographic characteristics, selected variables, and genotypes of the *IL17F* variants between the cases and controls were evaluated using the *t* test or Fisher exact test, as appropriate. The Hardy-Weinberg equilibrium was tested using the χ^2 goodness-of-fit test to compare observed genotype frequencies in asthmatic patients with those of controls. Associations between genotypes and risk of asthma were estimated by computing the ORs and their 95% CIs using logistic regression analyses for crude ORs and adjusted ORs, taking into account age, gender, and smoking status. Statistical significance was set at $P<.05$. The EM algorithm in SAS 9.1.3 PROC HAPLOTYPE was used to infer haplotype frequencies based on the observed genotypes. All statistical analyses were carried out using SAS 9.1.3 (SAS Institute). A 2-tailed *P* value <.05 was considered significant.

Results

Study Population

Demographic data and clinical characteristics of the study participants are shown in Table 1. No significant differences were observed between the cases and controls in terms of age, gender, or smoking. However, peripheral eosinophil counts, serum IgE, forced expiratory volume in the first second of expiration (FEV_1, % predicted), and ratio of FEV_1 to forced vital capacity (FVC) showed significant differences in the asthmatic group compared with the control group ($P<.0001$ for all comparisons; Table 1).

Table 2. Primers and Probe Sequences of 7488T/C and 9576A/G

SNP	SNP Type	Primer Type-Model	Sequences
9576A/G rs13209590	A/G	PCRU	CTCTAAAAATGTGAGTGTGCTGTC
		PCRL	TTACAGGAACAACAGGAGTATCG
		SNPU	GTGATTCTGTACGTGTCGCCCCTT
			CAGATTTCTGATCTCTTTTGC
7488T/C rs763780	T/C	PCRU	CATTTCTACAGCTTCTTCAGCTG
		PCRL	AGAAGGTGCTGGTGACTGTT
		SNPU	AGAGCGAGTGACGCATACTAGT
			GGATATGCACCTCTTACTGCACA

Abbreviation: SNP, single-nucleotide polymorphism.

Distribution of Alleles and Genotypes of Polymorphisms in IL17F

The observed genotype frequencies for rs13209590 and rs763780 in the controls were in Hardy-Weinberg equilibrium ($P\geq.30$; data not shown). The allele and genotype distributions of the polymorphisms in the cases and controls are shown in the Figure. In the single locus analyses, a significantly lower frequency of the C allele in rs763780 was observed in the control group ($P=.0142$). However, the allele distributions of rs13209590 were not significantly different between the control group and the case group

(*P*≥.11). Logistic regression analyses revealed that the rs763780 TC heterozygote was associated with a significantly increased risk of asthma (Table 3). When we combined the variant genotypes (rs763780 TC+CC) assuming a codominant genotype, we observed a similar trend to that of the rs763780 TT wild-type homozygote. Furthermore, multivariate analysis of the genotypes adjusted for age, gender, and smoking status confirmed this association (adjusted OR, 1.58 [95% CI, 1.06-2.36; *P*=.0148]; adjusted OR, 1.64 [95% CI, 1.10-2.45; *P*=.0217], respectively). However, no association was identified between the genotype of rs13209590 and risk of asthma.

Haplotype Analysis

When the 2 loci were combined and tested for haplotype inference using the SAS 9.1.3 PROC HAPLOTYPE program, 3 possible haplotypes were derived from the

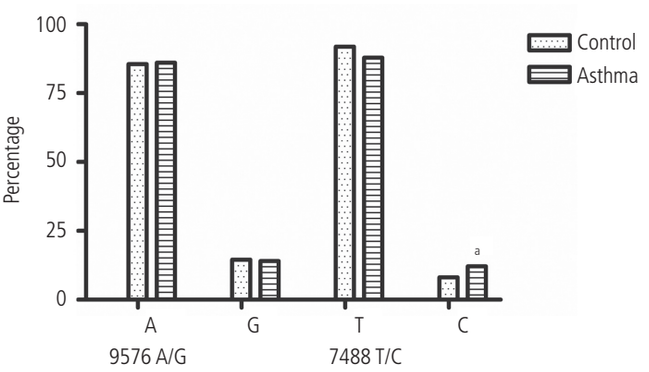

Figure. Allele distributions in polymorphisms of *IL17F*.
[a]*P* = .0142 (Fisher exact method for rs763780 in a 2 × 2 table)

Table 3. Logistic Regression Analysis of Associations Between Polymorphisms and Risk of Asthma

	Asthma		Control[a]		Crude Odds Ratio	Adjusted Odds Ratio
	No.	(%)	No.	(%)	(95% CI)	(95% CI)
9576A/G rs13209590						
AA	233	(73.2)	253	(72.1)	1	1
AG	81	(25.5)	94	(26.8)	0.94 (0.66-1.33)	0.95 (0.67-1.36)
GG	4	(1.2)	4	(1.1)	1.09 (0.27-4.47)	0.85 (0.19-3.81)
AG+GG	85	(26.7)	98	(27.9)	0.94 (0.67-1.32)	0.95 (0.67-1.34)
7488T/C rs763780						
TT	244	(76.7)	295	(83.8)	1	1
TC	71	(22.3)	57	(16.2)	1.51 (1.02-2.22)	1.58 (1.06-2.36)[b]
CC	3	(1.0)	0	(0)	NS	NS
TC+CC	74	(23.3)	57	(16.2)	1.57 (1.07-2.31)	1.64 (1.10-2.45)[c]

[a]Because of genotyping failure, the total number of controls for rs13209590 was 351. Age, gender, smoking status, and atopy were included in the modelto adjust for potential confounders.
[b]*P*=.0148.
[c]*P*=.0217.

Table 4. Haplotypes of the *IL17F* Gene in Control and Patient Groups

Haplotypes of IL17F		Allele Frequencies				
9576A/G rs13209590	7488T/C rs763780	Patients (n = 636)		Controls (n = 704)[a]		Adjusted Odds Ratio (95% CI)
		No.	%	No.	%	
9A	T	470	73.90	543	77.35	0.82 (0.63-1.06)
G	T	89	13.99	102	14.53	0.95 (0.69-1.30)
A	C	77	12.11	57	8.12	1.62 (1.11-2.35)[b]

[a]Because of genotyping failure, the total number of chromosomes for controls was 702. Age, gender, smoking status, and atopy were included in the model to adjust for potential confounders.
[b]*P* = .0115.

Table 5. Stratified Analyses Between 7488T/C rs763780 and Risk of Asthma[a]

Variables	Cases (n=318)		Control (n=352)		Adjusted	*P*
	TT	TC/CC	TT	TC/CC	OR (95% CI)	
Sex						
Male	98 (72.6)	37 (27.4)	165 (82.5)	35 (17.5)	1.79 (1.06-3.05)	.030
Female	146 (79.8)	37 (20.2)	130 (85.5)	22 (14.5)	1.44 (0.79-2.62)	.238
Log_{10}IgE, IU/mL[b]						
<1.85	93 (74.4)	32 (25.6)	251 (84.0)	48 (16.0)	1.35 (0.57-3.17)	.496
≥1.85	128 (80.0)	32 (20.0)	44 (84.6)	8 (15.4)	1.88 (1.10-3.22)	.021

Abbreviation: Ig, immunoglobulin.
[a]Adjusted for age, gender, and smoking.
[b]We assessed 351 controls and 285 patients for immunoglobulin E. Log_{10}IgE, log_{10}-transformed mean IgE levels.

known genotypes (Table 4). Compared with the most common haplotype A-T, the A-C haplotype was associated with an increased risk of asthma (adjusted OR, 1.62; 95% CI, 1.11-2.35). Because the prevalence of carriers of other haplotypes not containing the minor allele at rs763780 was not higher in the cases, this finding only reflects the individual association of rs763780 with asthma.

Association Between rs763780 and Asthma Phenotype

No differences in serum total IgE, FEV_1, or FEV_1/FVC values were observed between participants with different genotypes (data not shown). We also analyzed rs763780 genotypes after stratifying by gender and log_{10}-transformed IgE (< or ≥1.85 IU/mL). According to the mean level of log_{10}-transformed IgE (1.85 IU/mL) in the case group, we divided patients into 2 groups. As shown in Table 5, we found that the risk factor of rs763780 TC + CC was more pronounced in male patients (adjusted OR, 1.79; 95% CI, 1.06-3.05; *P*=.038) and patients with higher serum total IgE levels (≥1.85 IU/mL [mean of log_{10}IgE]; adjusted OR, 1.88 [95% CI, 1.10-3.22; *P*=.0213]).

Discussion

Our study revealed that the SNP rs763780 was associated with risk of asthma and that this association was exclusive to males and patients with higher IgE levels (≥1.85 IU/mL). The minor allele was more common in the asthma group and was largely present on 1 specific haplotype (A-C) (ie, the difference in allele frequency is the same as the difference in haplotype frequency).

Analysis of associations between polymorphisms in *IL17F* and asthma or asthma-related phenotypes in American white women [15] and Asian populations [14,16] revealed inconsistent results. Kawaguchi et al [14] found an inverse relationship between rs763780 and the risk of asthma in both men and women. Jin et al [16] failed to find any association between rs763780 and asthma in men and women. Ramsey et al [15] reported no association between rs763780 in *IL17F* and asthma in white women. Our gender-stratified analysis also confirmed that rs763780 was not associated with female asthma. Therefore, our findings are consistent with those of Ramsey et al. The reason for the gender-specific effect is unclear. Childhood asthma is more common in boys than in girls, while adult-onset asthma typically develops in middle age and is more common in women than in men.

Kawaguchi et al [14] also found that rs763780 TC exerts a protective effect against asthma in the Japanese population, although the differences were not statistically significant. The authors illustrated the exact mechanisms of the SNP in regulating asthma using in vitro functional experiments. We observed that the effect of the *IL17F* haplotype was due to the specific SNP constituting the haplotype and, therefore, provide no new information.

The importance of IgE-based mechanisms in asthma is supported by the impact of humanized anti-IgE monoclonal antibody treatments for asthma and other allergic diseases [21]. Our study indicates that the minor allele of rs763780 was associated with elevated IgE levels. However, the underlying mechanisms of this association have yet to be determined. Many studies now suggest that IL-17 is associated with IgE levels. Using a murine atopic dermatitis model, Matsushima et al [22] found that malfunction of tumor necrosis factor receptor–associated factor 3 interacting protein 2 caused hyper-IgE-emia and skin inflammation through the IL-17–mediated pathway [22]. IL-17 protein levels in the peripheral blood of affected female mice were 3.3-6.5–fold higher than those of unaffected mice. Conversely, few differences were observed between affected and unaffected male mice [22]. Patients with hyper-IgE syndrome (HIES) associated with atopic dermatitis and increased serum IgE levels and patients with signal transducer and activator of transcription protein (STAT3) mutations with HIES showed significantly lower T_H17 cell counts than patients with wild-type STAT3 and controls [23].

IL17F and *IL17* are close together in the chromosome and share 44% identity in the amino acid sequence (the highest similarity in the *IL17* family). *IL17F* may also be associated with the above models. The exact mechanism of the SNP in regulating IgE expression requires further investigation.

Our study is subject to a series of limitations. First, although our sample was large enough to detect significant differences, replication in additional cohorts is required to validate the association between *IL17F* polymorphisms and the progression of lung disease in asthmatic patients. Additionally, the implication of other *IL17F* polymorphisms needs to be tested in larger groups. Nevertheless, the association we observed is statistically significant ($P = .034$). Second, environmental factors other than smoking (eg, occupational exposure, pets, allergen exposure, and domestic endotoxin levels) may act as potential confounders in the analysis. Third, rigid adherence to an empirical significance level of $P < .05$ may be too conservative and obscure true-positive associations.

Conclusions

Our findings support the association between polymorphisms in *IL17F* and the risk of asthma in our sample of Han Chinese patients. To confirm the significance of polymorphisms in *IL17F*, future studies should be performed in larger samples. More extensive and better-designed studies using appropriate molecular and statistical methods are necessary to further analyze this association.

Acknowledgments

We thank all the study participants. We are also grateful to Drs. Sun PL, Li MM, and Yao X (Department of Respiratory Medicine, First Affiliated Hospital, Nanjing Medical University, Nanjing, China) for their help with the recruitment of volunteers.

References

1. Umetsu DT, Dekruyff RH. The regulation of allergy and asthma. Immunol Rev. 2006;212:238-55.
2. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet. 2008;372:1107-19.
3. Steinman L. A brief history of TH17, the first major revision in the TH1/TH2 hypothesis of T cell-mediated tissue damage. Nat Med. 2007;13:139-45.
4. Lloyd CM, Hessel EM. Functions of T cells in asthma: more than just T(H)2 cells. Nat Rev Immunol. 2010;10:838-48.
5. Fujiwara M, Hirose K, Kagami S, Takatori H, Wakashin H, Tamachi T, Watanabe N, Saito Y, Iwamoto I, Nakajima H. T-bet inhibits both TH2 cell-mediated eosinophil recruitment and TH17 cell-mediated neutrophil recruitment into the airways. J Allergy Clin Immunol. 2007;119:662-70.
6. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, Ceuppens JL. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? Respir Res. 2006;7:135.
7. Schmidt-Weber CB, Akdis M, Akdis CA. TH17 cells in the big picture of immunology. J Allergy Clin Immunol. 2007;120:247-54.
8. McKinley L, Alcorn JF, Peterson A, Dupont RB, Kapadia S, Logar A, Henry A, Irvin CG, Piganelli JD, Ray A, Kolls JK. TH17 cells mediate steroid-resistant airway inflammation and airway hyperresponsiveness in mice. J Immunol. 2008;181:4089-97.
9. Kawaguchi M, Onuchic LF, Li XD, Essayan DM, Schroeder J, Xiao HQ, Liu MC, Krishnaswamy G, Germino G, Huang SK. Identification of a novel cytokine, ML-1, and its expression in subjects with asthma. J Immunol. 2001;167:4430-5.
10. Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z, Dong C. Regulation of inflammatory responses by IL-17F. J Exp Med. 2008;205:1063-75.
11. Al-Ramli W, Préfontaine D, Chouiali F, Martin JG, Olivenstein R, Lemière C, Hamid Q. T(H)17-associated cytokines (IL-17A and IL-17F) in severe asthma. J Allergy Clin Immunol. 2009;123:1185-7
12. Qian FH, Zhang Q, Zhou LF, Jin GF, Bai JL, Yin KS. Polymorphisms in toll-like receptor 2 subfamily and risk of asthma: a case-control analysis in a Chinese population. J Investig Allergol Clin Immunol. 2010;20:340-6.
13. Haagerup A, Bjerke T, Schiotz PO, Binderup HG, Dahl R, Kruse TA. Asthma and atopy — a total genome scan for susceptibility genes. Allergy. 2002;57:680-6.
14. Kawaguchi M, Takahashi D, Hizawa N, Suzuki S, Matsukura S, Kokubu F, Maeda Y, Fukui Y, Konno S, Huang SK, Nishimura M, Adachi M. Il-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity. J Allergy Clin Immunol. 2006;117:795-801.
15. Ramsey CD, Lazarus R, Camargo CA Jr, Weiss ST, Celedón JC. Polymorphisms in the interleukin 17f gene (IL17F) and asthma. Genes Immun. 2005;6:236-41.
16. Jin EH, Choi EY, Yang JY, Chung HT, Yang YS. Significant association between IL-17F promoter region polymorphism and susceptibility to asthma in a Korean population. Int Arch Allergy Immunol. 2010;155:106-10.
17. National Institutes of Health, National Heart, Lung and Blood Institute. GINA workshop report, Global strategy for asthma management and prevention (2005 Update). [Cited Jan 16, 2006]. Available from: www. ginasthma.com.
18. Wu X, Gu J, Grossman HB, Amos CI, Etzel C, Huang M, Zhang Q, Millikan RE, Lerner S, Dinney CP, Spitz MR. Bladder cancer predisposition: a multigenic approach to DNA-repair and cell cycle-control genes. Am J Hum Genet. 2006;78:464-79.
19. Qian FH, Zhang Q, Zhou LF, Liu H, Huang M, Zhang XL, Yin KS. High sensitivity C-reactive protein: a predicative marker in severe asthma. Respirology. 2008;15:664-9.
20. Olson JE, Ma CX, Pelleymounter LL, Schaid DJ, Pankratz VS, Vierkant RA, Fredericksen ZS, Ingle JN, Wu Y, Couch F, Sellers TA, Weinshilboum RM, Vachon CM. A comprehensive examination of CYP19 variation and risk of breast cancer using two haplotype tagging approaches. Cancer Epidemiol Biomarkers Prev. 2007;16:623-5.
21. Marcus P. Practice Management Committee, American College of Chest Physicians. Incorporating anti-IgE (omalizumab) therapy into pulmonary medicine practice: practice management implications. Chest. 2006;129:466-74.

22. Matsushima Y, Kikkawa Y, Takada T, Matsuoka K, Seki Y, Yoshida H, Minegishi Y, Karasuyama H, Yonekawa H. An atopic dermatitis-like skin disease with hyper-IgE-emia develops in mice carrying a spontaneous recessive point mutation in the Traf3ip2 (Act1/CIKS) gene. J Immunol. 2010;185:2340-9.
23. Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, Rieber N, Cremer R, Maass E, Dopfer R, Reichenbach J, Wahn V, Hoenig M, Jansson AF, Roesen-Wolff A, Schaub B, Seger R, Hill HR, Ochs HD, Torgerson TR, Belohradsky BH, Renner ED. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. J Allergy Clin Immunol. 2010;126:611-7.

Manuscript received October 6, 2011; accepted for publication February 24, 2012.

Fen-hong Qian

Department of Respiratory Medicine
Affiliated Hospital, Jiangsu University
Zhenjiang
Jiangsu, China
E-mail: zhaoqian604@yahoo.com.cn