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Jiankai Feng MD, Caiji Zhang MD, Zongguo Wang MD, Qian Li MD, Jie Li MM & Hongling Wang MM

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ORIGINAL ARTICLE

Association between CD14 gene promoter polymorphisms with serum total-IgE and eosinophil levels in atopic and non-atopic asthma patients in a Chinese Han populationJiankai Feng, MD^{1*}, Caiji Zhang, MD^{2*}, Zongguo Wang, MD^{3*}, Qian Li, MD², Jie Li, MM², and Hongling Wang, MM²¹Clinical Laboratory Medicine, Yan Tai Affiliated Hospital of Binzhou Medical University, Yantai, China, ²Center of Laboratory Medicine, the Affiliated Yuhuangding Hospital of Qingdao University Medical College, Yantai, China, and ³Yantai Municipal Center for Disease Control and Prevention, Yantai, China**Abstract**

Objective: The aim of this study was to investigate the association between CD14 gene promoter SNPs with serum total-IgE and eosinophil levels in atopic asthma and non-atopic asthma in Chinese Han. **Methods:** A total of 152 patients with asthma were divided into atopic asthma ($n = 100$) and non-atopic asthma ($n = 52$) groups for this study. Six CD14 gene SNPs were analyzed using PCR and gene sequencing. Serum total-IgE and eosinophil levels were measured. The association between genotype frequencies of the CD14 gene loci with total-IgE and eosinophil levels in atopic asthma and non-atopic asthma was evaluated by the ANOVA test method. Hundred and sixteen healthy subjects constitute the control group. **Results:** We found that serum total-IgE and eosinophil levels were significantly higher in individuals with atopic asthma when compared to individuals with non-atopic asthma ($p < 0.01$). For non-atopic asthma, the total-IgE levels of the heterozygous genotypes were significantly higher than the corresponding levels for the homozygous genotypes in CD14-260C>T, CD-651C>T, CD-911A>C and CD-1247A>G ($p < 0.01$). In atopic asthma, there was no statistical significance for either serum total-IgE or eosinophil levels among the genotypes of the CD14 gene SNPs. In addition, allele A frequency of CD14-1247A>G was significantly different between the atopic asthma and non-atopic asthma groups ($p = 0.025$). **Conclusions:** There was a statistical association between the serum total-IgE level and the CD14 gene promoter SNPs in the non-atopic asthma group. The eosinophil level was not found to be statistically associated with the CD14 gene promoter SNPs in either the atopic asthma or non-atopic asthma groups.

Keywords

Atopic asthma, CD14, eosinophil, non-atopic asthma, serum total-IgE, single nucleotide polymorphism

History

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Introduction

Asthma is a complex disease with a pathogenesis related to both environmental and genetic factors [1,2]. Asthma runs strongly in families and is approximately half due to environmental factors and half due to genetic susceptibility. The asthma diagnosed in children and young adults is most often associated with allergens in the environment; however, some types of asthma are not strongly correlated with allergens. The type of asthma associated with allergens is called atopic asthma, whereas the type that is not connected to allergens is called non-atopic asthma.

CD14 is a multifunctional receptor found on macrophages and monocytes that bind endotoxins and other bacterial wall components. The CD14 gene is located on chromosome 5q31.3, a region associated with asthma in genome-wide linkage studies [3]. Polymorphisms of CD14 have been shown

to influence serum IgE levels and skin prick test responses to allergens [4,5]. Numerous studies have been conducted to investigate the relationship between CD14 variants and total IgE levels [6]. CD14 acts as a co-receptor for the detection of bacterial lipopolysaccharides (LPS). CD14 promotes immune activation by facilitating the presentation of LPS to Toll-like receptors 4 (TLR4) [7], which trigger IL-12 and IL-18 signaling in addition to interferon-gamma production. Altered expressions of CD14 may affect the proportion of Th1 to Th2 cells, thereby influencing IgE responses [8] and associated inflammatory phenotypes in allergic conditions such as asthma. Whereas several genetic polymorphisms in the CD14 gene have been examined in relation to allergic disease risk, a consistent link has not been established. A recent review found no evidence of a role played by a single nucleotide polymorphism (SNP) in the CD14 gene and the risk of childhood asthma among Caucasian children [9]. In contrast, a meta-analysis of the widely studied CD14-260C>T promoter polymorphism and atopic asthma found a significant protective effect for carriers of the TT or CT genotype compared with the CC genotype [10].

*These authors contributed equally to this work.

Correspondence: Dr Jiankai Feng, Clinical Laboratory Medicine, Yan Tai Affiliated Hospital of Binzhou Medical University, JinBu Street 717, MuPing District, YanTai City, Yantai 264000, China. Tel: +86-535-4770361. Fax: +86-535-4770360. E-mail: fengtao7668@163.com

Different genetic backgrounds and environmental exposures can affect the pathogenesis of asthma. Therefore, asthma susceptibility genes in different ethnic and regional populations are different. In the present study, we first used gene sequencing and made comparisons with reference genes. We investigated six genetic loci polymorphisms of the CD14 promoter region that are associated with total-IgE and eosinophil levels in atopic asthma and non-atopic asthma. At the same time, the genotypes and alleles of every genetic loci were statistically analyzed between asthma patients, which included patients with both atopic asthma and non-atopic asthma, and the control groups. Both the study subjects and the healthy control subjects are Chinese Han people who live in the coastal city of Yantai, China.

Materials and methods

Study subjects

A total of 152 patients with asthma (consisting of 84 males and 68 females) were recruited from the outpatient department of Yantai Yuhuangding Hospital in Yantai, Shandong Province, China. The average age of the patients was 23.7 ± 20.6 years. At the same time, 116 control subjects were recruited from the same hospital. They were people to do a healthy physical examination in the hospital. The average age of the controls was 18.7 ± 12.9 years. Through the results of physical examination and allergy tests and the questionnaire investigation, we knew the controls had no history of asthma, rhinitis or other chronic pulmonary diseases and were matched with the asthma patients according to ethnic origin and residential area. All study subjects were from a Chinese Han population living in the coastal area of Yantai, China. Informed consent was obtained from all participating subjects. All study procedures for the participants were approved by the Affiliated Yuhuangding Hospital of Qingdao University Medical.

Asthma was diagnosed according to the Global Initiative for Asthma (GINA) guideline. The asthma patients and controls were interviewed by investigators using the same structured questionnaire. A single blood sample was collected by venipuncture to measure serum total-IgE and eosinophil levels and for DNA isolation. The specific IgE was measured using the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). S-IgE levels then were determined for inhaled allergens, food allergens, house dust, *Dermatophagoides farinae*, cat dander and dog dander. Values of 0.35 KU/L or greater were considered positive. Patients with asthmatic symptoms were measured using skin prick testing, and those who showed a positive reaction to at least one S-IgE level and skin prick testing were classified as having atopic asthma ($n = 100$). Patients with asthmatic symptoms but no allergy symptoms, no personal allergy history, and negative results for both the S-IgE level and skin prick tests were classified as having non-atopic asthma ($n = 52$). This classification was conducted in accordance with the principles of the Declaration of Helsinki (2008). All participants also received chest X-rays and pulmonary function tests, and measurements of weight, height and blood pressure.

Total serum IgE and eosinophil measurement

Total serum IgE levels were measured by immune turbidimetry using the automatic special protein instrument BNII

(Siemens Dade Behring, Marburg, Germany). Eosinophil levels were measured with the automatic blood analyzer XE5000 (Sysmex Corporation, Kobe, Japan).

DNA extraction

Genomic DNA was extracted from 3 mL of EDTA containing whole blood collected from the study subjects and healthy controls using a commercial genomic DNA extraction kit (Qiagen, Hilden, Germany) according to the manufacturer instructions. The DNA was stored at -80°C until gene amplification.

Gene amplification and sequencing

Genomic DNA extracted from whole-blood samples was amplified with a hot start polymerase chain reaction (PCR) using the Premix Ex Taq™ Hot Start Version Kit (TaKaRa Sara USA Inc., Berkeley, CA). Forward primer: 5'-GGCTGTTGTAAATGCGTAGC-3'. Reverse primer: 5'-CCTCCTCTGTGAACCCTGAT-3'. PCR reaction mixture system (total 50 μL): hot start version 25 μL , forward primer 1.5 μL , reverse primer 1.5 μL , genomic DNA 2.0 μL and sterilized distilled water 20 μL . PCR reaction conditions: initial denaturation at 95°C for 5 min and temperature cycling set at 98°C for 10 s, 55°C for 40 s and 72°C for 60 s for 30 cycles, followed by a final extension at 72°C for 10 min. PCR products were expected to be 1203 bp, and their sizes were confirmed by agarose gel electrophoresis prior to their storage at -80°C .

All PCR products were used for DNA sequencing with the Sanger dideoxy chain termination method by Shanghai Sangon Biotechnology (China).

SNP genotyping

Genotyping of six SNPs for the CD14 gene promoter was performed using gene analysis software LaserGene7.0 (DNASar Company, Madison, WI). The six SNPs loci were CD14-260C > T(rs2569190), CD14-651C > T(rs744455), CD14-775C > G (rs75652866), CD14-911A > C(rs744454), CD14-1227T > G(rs744451) and CD14-1247A > G(rs2569191). The genotyping of all six CD14 SNPs was confirmed by two researchers. A *Homo sapiens* CD14 gene molecule reference sequence was obtained from GenBank (NC00005.10 chromosome 5 reference GRCh38 Primary Assembly).

Statistical analysis

Statistical analyses were performed using the SPSS 17.0 (SPSS, Inc., Chicago, IL) package software. Study subject demographics and disease characteristics were summarized using descriptive statistics. Continuous variables are reported as the mean $\pm$ standard deviation (SD). The χ^2 test was used to examine the deviation of genotype frequencies from the Hardy-Weinberg equilibrium and determine genotype and allele frequencies between the asthma patients with the healthy control groups as well as between the atopic asthma and non-atopic asthma groups. A *t*-test was used to compare total-IgE and eosinophil levels between the atopic asthma and non-atopic asthma patients. A one-way analysis of variance

Table 1. Characteristics of asthma and control groups.

Characteristics	All asthma (n = 152)	Atopic asthma (n = 100)	Non-atopic asthma (n = 52)	Control (n = 116)
Age (years)	23.7 ± 20.6	18.9 ± 16.6	33.0 ± 24.2	18.7 ± 12.9
Gender				
Male	84 (55.3%)	58 (58.0%)	26 (50.0%)	68 (58.6%)
Female	68 (44.7%)	42 (42.0%)	26 (50.0%)	48 (41.4%)
Total-IgE (IU/mL)	223.0 ± 355.4	300.4 ± 413.9	74.1 ± 84.3	
Eosinophil (×10 ⁹)	0.23 ± 0.19	0.26 ± 0.19	0.17 ± 0.16	
Skin prick test (Asthma)				
Positive	100	100	0	0
Negative	52	0	52	116
Specific-IgE (KU/L)				
≥0.35		100	0	0

Table 2. Gene CD14 genotype frequency in the asthma and control groups.

Gene loci	Genotypes	Asthma (n = 152) (%)	Control (n = 116) (%)	χ ²	p Value
CD14-260	CC	20 (13.2)	14 (12.1)	0.107	0.948
	CT	76 (50.0)	60 (51.7)		
	TT	56 (36.8)	42 (36.2)		
CD14-651	CC	82 (53.9)	52 (44.8)	3.952	0.139
	CT	58 (38.2)	58 (50.0)		
	TT	12 (7.9)	6 (5.2)		
CD14-911	AA	82 (53.9)	52 (44.8)	3.952	0.139
	AC	58 (38.2)	58 (50.0)		
	CC	12 (7.9)	6 (5.2)		
CD14-1247	AA	20 (13.2)	14 (12.1)	1.135	0.567
	AG	74 (48.7)	64 (55.2)		
	GG	58 (38.2)	38 (32.8)		

(ANOVA) was used to compare total-IgE and eosinophil levels for different genotypes of each SNP loci. Fisher's least-significant difference from one-way ANOVA was used for normally distributed continuous variables and Tamhane's T2 test was used for non-normally distributed continuous variables. Two-sided *p*-values at the 0.05 level were used to determine statistical significance.

Results

Characteristics of study subjects

The characteristics of the 152 asthma patients and 116 healthy controls are shown in Table 1.

Genotype and allele frequency

The genotype and allele frequency of gene CD14 promoter SNPs in all asthma groups and the healthy control group are shown in Tables 2 and 3, respectively. There were no statistically significant differences among the CD14-260C>T, CD-651C>T, CD-911A>C and CD-1247A>G genotype and allele frequencies between the asthma and control groups (*p*>0.05). It was worth mentioning that genotypes of CD-651C>T and CD-911A>C were associated. In all study subjects, the CD-651C>T genotypes were homozygous CC when the CD-911A>C genotypes were homozygous AA; the CD-651C>T genotypes were

homozygous TT when the CD-911A>C genotypes were homozygous CC and the CD-651C>T genotypes were heterozygous CT when the CD-911A>C genotypes were heterozygous AC. Therefore, the genotype and allele frequencies were completely consistent.

The genotype and allele frequency of CD14 gene promoter SNPs for the atopic asthma and non-atopic asthma groups are shown in Tables 4 and 5, respectively. No significant differences were observed among the CD14-260C>T, CD-651C>T, CD-911A>C and CD-1247A>G genotype frequencies measured between the two groups (*p*>0.05). Only the allele frequencies for CD14-1247A>G had significant differences in four CD14 gene loci between the atopic asthma and non-atopic asthma groups (*p*=0.025). The minor allele A frequency measured in the atopic asthma group (42%) was higher than allele frequency measured in the non-atopic asthma group (28%).

In addition, we found that the genotype of CD14-775C>G locus was homozygous CC and the genotype of CD14-1227T>G locus was homozygous for TT in the asthma group and the control group. So their genotype frequencies were not analyzed in the table.

Total-IgE and eosinophil level

Total-IgE and eosinophil levels were significantly higher in the atopic asthma patients than the non-atopic asthma patients (*p*<0.001 and *p*=0.009, respectively; Table 6). In atopic asthma patients, total-IgE and eosinophil levels were different. However, these differences were not statistically significant for the different genotypes of the four CD14 gene loci (all *p*>0.05; Table 7). In the non-atopic asthma patients, there were no significant differences for eosinophil levels among the different genotypes for the four CD14 gene loci (*p*>0.05; Table 8), but there were statistically significant differences for total-IgE levels among the different genotypes of the four CD14 gene loci. For every CD14 gene loci, the total-IgE levels of the heterozygous genotypes were significantly higher than the homozygous genotypes (*p*<0.01).

Discussion

Asthma may develop as a result of interactions between environmental influences and individual's genetic characteristics. The monocyte differentiation antigen 14 (CD14) gene is becoming one of the most widely studied genes associated with asthma. The influence of CD14 on the congenital immune

Table 3. Gene CD14 allele frequency in the asthma and control groups.

Gene loci	Alleles	Asthma (<i>n</i> = 152) (%)	Control (<i>n</i> = 116) (%)	χ^2	<i>p</i>	OR (95% CI)
CD14-260	C	116 (38.2)	88 (37.9)	0.003	0.957	1.01 (0.71–1.44)
	T	188 (61.8)	144 (62.1)			
CD14-651	C	222 (73.0)	162 (69.8)	0.663	0.416	1.17 (0.80–1.71)
	T	82 (27.0)	70 (30.2)			
CD14-911	A	222 (73.0)	162 (69.8)	0.663	0.416	1.17 (0.80–1.71)
	C	82 (27.0)	70 (30.2)			
CD14-1247	A	114 (37.5)	92 (39.7)	0.258	0.611	0.91 (0.64–1.30)
	G	190 (62.5)	140 (60.3)			

Table 4. Gene CD14 genotype frequency in the non-atopic asthma and atopic asthma groups.

Gene loci	Genotypes	Non-atopic asthma (<i>n</i> = 52) (%)	Atopic asthma (<i>n</i> = 100) (%)	χ^2	<i>p</i>
CD14-260	CC	4 (7.7)	16 (16.0)	3.889	0.143
	CT	24 (46.2)	52 (52.0)		
	TT	24 (46.2)	32 (32.0)		
CD14-651	CC	28 (53.8)	54 (54.0)	0.006	0.997
	CT	20 (38.5)	38 (38.0)		
	TT	4 (7.7)	8 (8.0)		
CD14-911	AA	28 (53.8)	54 (54.0)	0.006	0.997
	AC	20 (38.5)	38 (38.0)		
	CC	4 (7.7)	8 (8.0)		
CD14-1247	AA	4 (7.7)	16 (16.0)	5.359	0.069
	AG	22 (42.3)	52 (52.0)		
	GG	26 (50.0)	32 (32.0)		

Table 5. Gene CD14 allele frequency in the non-atopic asthma and atopic asthma groups.

Gene loci	Allele	Non-atopic asthma (<i>n</i> = 52) (%)	Atopic asthma (<i>n</i> = 100)	χ^2	<i>p</i>	OR (95% CI)
CD14-260	C	32 (30.8)	84 (42.0)	3.657	0.056	0.61 (0.37–1.01)
	T	72 (69.2)	116 (58.0)			
CD14-651	C	76 (73.1)	146 (73.0)	0.000	0.989	1.00 (0.59–1.71)
	T	28 (26.9)	54 (27.0)			
CD14-911	A	76 (73.1)	146 (73.0)	0.000	0.989	1.00 (0.59–1.71)
	C	28 (26.9)	54 (27.0)			
CD14-1247	A	30 (28.8)	84 (42.0)	5.051	0.025	0.56 (0.34–0.93)
	G	74 (71.2)	116 (58.0)			

response is determined based on gene expression levels [11]. Because the promoter is known to play an important role in regulating gene expression, studies examining CD14 gene polymorphisms focus primarily on the promoter region. The CD14-260C>T polymorphism was associated with serum CD14 levels as well as the phenotypes of patients with allergies [12,13]. In this study, we investigated six SNPs in the promoter region of CD14 in relation to asthma, atopic asthma and non-atopic asthma in Chinese Han populations living in coastal areas.

A meta-analysis reviewing studies of Asians found a non-significant association between the CD14-260C>T polymorphism and overall asthma [10]. In our study, the genotype frequencies of CD14-260C>T, CD14-651C>T, CD14-911A>C and CD14-1247A>G did not have statistically significant differences between the asthma patients and the

control groups, and there were also no significant differences between the atopic asthma and non-atopic asthma groups. The results were consistent with a recent study reporting that the distributions of the CD14-260C>T genotypes (CC, CT, TT) did not differ significantly between the asthma and control groups [14–16]. It is worth mentioning that genotype CC of CD14-651C>T and AA of CD14-911A>C, TT of CD14-651C>T with CC of CD14-911A>C, and AC of CD14-651C>T and AC of CD14-911A>C would always appear at the same time. Therefore, their genotype frequencies were consistent. The genotypes of CD14-775C>G (rs75652866) were all homozygote CC, and the genotypes of CD14-1227T>G (rs5744451) were all homozygote TT in asthma patients and the control group. Literature about the two loci genotypes did not include a study of the relationship with asthma.

Table 6. Total-IgE and eosinophil levels in the atopic asthma and non-atopic asthma groups.

	Atopic asthma (n = 100)	Non-atopic asthma (n = 52)	t	p
Total-IgE (KU/L)	301.8 ± 413.0	74.1 ± 84.3	5.304	0.000
Eosinophil (×10 ⁹)	0.296 ± 0.315	0.173 ± 0.159	2.639	0.009

Table 7. Total-IgE and eosinophil levels of different CD14 genotypes in atopic asthma.

Gene loci	Genotype	n = 100	Total-IgE (KU/L)	F	p	Eosinophil (×10 ⁹)	F	p
CD14-260	CC	16	192.2 ± 66.2	1.086	0.342	0.24 ± 0.16	0.708	0.495
	CT	52	290.5 ± 351.6			0.28 ± 0.19		
	TT	32	374.9 ± 572.1			0.35 ± 0.49		
CD14-651	CC	54	360.2 ± 541.0	1.183	0.311	0.28 ± 0.39	0.890	0.414
	CT	38	230.7 ± 162.0			0.34 ± 0.19		
	TT	8	245.0 ± 28.4			0.20 ± 0.10		
CD14-911	AA	54	360.2 ± 541.0	1.183	0.311	0.28 ± 0.39	0.890	0.414
	AC	38	230.7 ± 162.0			0.34 ± 0.19		
	CC	8	245.0 ± 28.4			0.20 ± 0.10		
CD14-1247	AA	16	192.2 ± 66.2	1.086	0.342	0.24 ± 0.16	0.708	0.495
	AG	52	290.5 ± 351.6			0.28 ± 0.19		
	GG	32	374.9 ± 413.0			0.35 ± 0.49		

Table 8. Total-IgE and eosinophil levels of different CD14 genotypes in the non-atopic asthma group.

Gene loci	Genotype	n = 52	Total-IgE (KU/L)	F	p	Eosinophil (×10 ⁹)	F	p
CD14-260	CC	4	34.8 ± 20.2	5.974	0.005	0.02 ± 0.01	2.167	0.125
	CT	24	114.0 ± 109.2			0.19 ± 0.14		
	TT	24	40.7 ± 26.6			0.18 ± 0.18		
CD14-651	CC	28	37.4 ± 25.9	11.241	0.000	0.19 ± 0.18	2.129	0.130
	CT	20	133.3 ± 109.9			0.18 ± 0.12		
	TT	4	34.8 ± 20.2			0.02 ± 0.01		
CD14-911	AA	28	37.4 ± 25.9	11.241	0.000	0.19 ± 0.18	2.129	0.130
	AC	20	133.3 ± 109.9			0.18 ± 0.12		
	CC	4	34.8 ± 20.2			0.02 ± 0.01		
CD14-1247	AA	4	34.8 ± 20.2	8.143	0.001	0.02 ± 0.01	2.415	0.100
	AG	22	122.8 ± 110.0			0.20 ± 0.14		
	GG	26	38.9 ± 26.3			0.17 ± 0.17		

No significant differences in the allele frequencies of the four CD14 gene loci were found in a comparison between the asthma group and normal control group. These results were consistent with a recent study [15,16]. While the allele frequencies of CD14-260C>T, CD14-651C>T and CD14-911A>C were not significantly different between the atopic and non-atopic asthma groups, the CD14-1247A>G allele frequencies were different ($p=0.025$). The A allele was associated with atopic asthma, with an A allele frequency of CD14-1247A>G measured at 42% in the atopic asthma group and at 28.8% in the non-atopic asthma group. These results were not found in the published literature and could be associated with the different ethnic and regional living situations of the research subjects.

In one study, there was a significant association between the CD14-260C>T SNP and serum total-IgE level in asthma [17]. In another research study, no correlation between CD14-260C>T SNP and serum total-IgE levels was found [18]. The conflicts in these results may be due to the heterogeneity of

the study subjects. In another study, the CD14-260C>T genotype was associated with total-IgE levels, and this association was found to change according to changing levels of endotoxin exposure [19]. Therefore, we divided asthma patients into two groups (atopic asthma and non-atopic asthma) according to whether allergens were detected to reduce the heterogeneity of the study subjects. In our study, total-IgE and eosinophil levels were significantly higher in the atopic asthma group than in the non-atopic asthma group ($p<0.01$). In the atopic asthma group, total-IgE and eosinophil levels were not associated with the genotypes of four CD14 gene SNPs ($p>0.05$). However, in non-atopic asthma, the total-IgE levels were statistically associated with the genotypes of four CD14 gene SNPs ($p<0.01$) and significantly higher in the heterozygous genotypes of every SNP when compared to the two homozygous genotypes. This result conflicts with recent researches for CD14-260C>T [14,20,21]. However, there was no statistical association between eosinophil level and the genotypes of four CD14

gene SNPs in the non-atopic asthma group. This result conflicts with recent research [14]. Therefore, different types of asthma (atopic and non-atopic) may have different pathogenesis and be related to race as well as living environment.

The literature which study association between asthma and CD14 SNPs (CD14-651C>T-911A>C and -1247A>G) is less. An analysis of Japanese elementary school children reported that day care significantly decreased total-IgE levels and mite-specific IgE levels, and rate of atopy in individuals with the CT or TT genotype, but not in those with the CC genotype, and the interaction between the CD14-651C>T (rs5744455) polymorphism and day care [22].

Conclusion

In summary, our study demonstrated a significant association between serum total-IgE levels and CD14 gene promoter SNPs in individuals with non-atopic asthma. Eosinophil levels were not associated statistically with CD14 gene promoter SNPs in either the atopic asthma or non-atopic asthma groups. The association of the CD14 gene polymorphism with atopic or non-atopic disease may be strongly associated with race and living environment. Our future studies will focus on the association of the CD14 gene polymorphism and the severity of asthma disease, as well as allergen type (inhaled and ingested allergens). The eventual identification of more asthma susceptibility genes will provide better insight into the pathogenesis of asthma as well as early diagnosis methods for individuals at risk for asthma.

Declaration of interest

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