ORIGINAL ARTICLE

Polymorphisms in *IL4* and *IL4RA* Confer Susceptibility to Asthma

AA Amirzargar,[1,2] M Movahedi,[3] N Rezaei,[4,5] B Moradi,[1] S Dorkhosh,[1] M Mahloji,[3] SA Mahdaviani[3]

[1] Immunogenetic Laboratory, Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2] Molecular Immunology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Allergy and Clinical Immunology, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[4] Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran
[5] Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: Asthma is a complex disease that is caused by genetic and environmental factors. The production of interleukin (IL)-4, which can influence mast cell responsiveness to immunoglobulin (Ig) E–mediated signaling, could be modified by genetic variants in the IL-4 promoter.
Objective: To investigate the association between the IL-4 and IL-4RA promoter polymorphisms and asthma in a sample of Iranian patients.
Methods: We used polymerase chain reaction with sequence-specific primers to investigate the allele and genotype frequencies of 2 polymorphic genes coding for IL-4 and IL-4RA in 59 Iranian patients with asthma and 139 healthy controls.
Results: The most frequent genotypes in the patient group were IL-4 TC (–590), IL-4 TC (–33), IL-4 GT (–1098), and IL-4RA GA (+1902). In contrast, the frequencies of IL-4 CC (–590), IL-4 CC (–33), IL-4 TT (–1098), and IL-4RA AA (+1902) were significantly lower in the patient group than in the control group. The most frequent haplotypes in our patients were IL-4 TCT and GTC at positions –1098, –590, –33. The mean total serum IgE level in patients with the TTT/GCC genotype was 258.8 IU/mL, which was significantly higher than the 95.4 IU/mL observed for other genotypes.
Conclusion: We showed a strong association between the polymorphisms of the IL-4 gene promoter at positions –590, –33 and –1098 and bronchial asthma. We also demonstrated an association between their haplotypes and serum total IgE.

Key words: Asthma. Genetic polymorphism. IL-4. IgE.

Resumen

Antecedente: El asma es una patología compleja que está causada por factores genéticos y ambientales. La producción de interleucina (IL) 4, que puede influenciar la receptividad del mastocito a la señalización mediada por inmunoglobulina (Ig) E, podría modificarse por variantes genéticas en el promotor de la IL-4.
Objetivo: Investigar la asociación entre los polimorfismos del promotor de IL-4 e IL-4RA y el asma en una muestra de pacientes Iraníes.
Métodos: Empleamos la reacción en cadena de la polimerasa con primers específicos de secuencia para investigar las frecuencias de los alelos y de los genotipos de 2 genes polimórficos codificantes para IL-4 e IL-4RA en 59 pacientes iraníes con asma y en 139 sujetos sanos control.
Resultados: Los genotipos más frecuentes en el grupo de los pacientes fue IL-4 TC (–590), IL-4 TC (–33), IL-4 GT (–1098), e IL-4RA GA (+1902). Al contrario, las frecuencias de IL-4 CC (-590), IL-4 CC (–33), IL-4 TT (–1098), y IL-4RA AA (+1902) fueron significativamente inferiores en el grupo de los pacientes que en el grupo control. Los haplotipos más frecuentes en nuestros pacientes fueron IL-4 TCT y GTC para las posiciones –1098, –590, –33. La media de los niveles de IgE sérica total en los pacientes con el genotipo TTT/GCC fue 258,8 IU/mL, significativamente mayor que los 95,4 IU/mL que se observaron para otros genotipos.
Conclusión: Observamos una asociación fuerte entre los polimorfismos del promotor del gen IL-4 en las posiciones –590, –33 y –1098 y el asma bronquial. Además, demostramos una asociación entre sus haplotipos y la IgE sérica total.

Palabras clave: Asma. Polimorfismo genético. IL-4. IgE.

© 2009 Esmon Publicidad

Introduction

Asthma is a common respiratory disease that is caused by acute and chronic inflammation of the airways and leads to variable bronchial obstruction [1,2]. Bronchial hyperresponsiveness and increased total serum immunoglobulin (Ig) E levels are prominent characteristics of the asthma phenotype [1,2], and both have a strong genetic component [3-6].

Stimulation of interleukin (IL)-4 can influence mast cell responsiveness to IgE-mediated signaling [7], whereas IL-4 gene transcription can be modified by genetic variants in the *IL-4* promoter. Thus it could be hypothesized that sequence variants of the *IL-4* gene are associated with the asthma phenotype. However, such an association remains controversial [8-10]. The IL-4 receptor α subunit (*IL-4 RA*) is a component of both the IL-4 and IL-13 receptor complexes. It has also been suggested that polymorphisms in *IL-4 RA* could be associated with changes in total serum IgE levels and asthma [11].

The controversial results on this topic in the literature [8-10] and racial/ethnic differences in asthma-related loci [12] led us to investigate the association between these polymorphisms and asthma in a sample of Iranian patients and controls.

Materials and Methods

Patients and Controls

This project was approved by the Ethics Committee of Tehran University of Medical Sciences. Informed consent was obtained from all participants. The sample comprised 59 individuals with asthma who were randomly selected from a group of asthmatic patients referred to the Asthma and Allergy Clinic of the Children's Medical Center Hospital, Tehran, Iran, during the year 2007 [13,14]. The diagnosis of asthma was based on clinical history, physical examination, and pulmonary function tests (PFT) (forced expiratory volume in 1 s [FEV_1]). We followed the guidelines of the National Asthma Education and Prevention program (Expert Panel Report-3) [15], and patients were examined for a history of breathlessness and wheezing. We also applied skin prick tests on all patients using a panel of common local environmental allergens including house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), animal dander (dog, cat), grasses, tree pollens, weeds, cockroach, and *Alternaria alternata* (Stallergenes, Antony, France). Positive (histamine 1 mg/mL) and negative (normal saline) controls were used. The wheal diameters were recorded after 15 minutes. The skin prick test was regarded as positive if the wheal of the test allergen was ≥3 mm greater than the reaction to the negative control.

The control population comprised 139 randomly selected healthy blood donors from Iranian blood transfusion organizations [16].

Genotyping

DNA sampling and genotyping were performed as described elsewhere [13,14]. Briefly, cytokine type was determined using polymerase chain reaction with sequence-specific primers (PCR-SSP) (Heidelberg cytokine gene polymorphism SSP kit Heidelberg University, Heidelberg, Germany). Amplification was carried out using a Techne Flexigene thermal cycler (Roche, Cambridge, UK). The presence or absence of PCR products was visualized using 2% agarose gel electrophoresis. After electrophoresis, the gel was placed on a UV transilluminator and a photograph was taken for interpretation and documentation. Each of the primer mixes contained a control primer pair that amplified either a part of the ß-globin gene or a part of the C-reactive protein (CRP) gene. The ß-globin control primers produced an 89-base pair (bp) fragment, while the primer pairs amplifying the *CRP* gene produced a 440-bp amplicon [16]. The allele and genotype frequencies of *IL-4* (G/T –1098, C/T –590, C/T –33), and *IL-4 RA* (G/A +1902) genes were determined

Statistical Analysis

Allele frequencies were estimated by direct gene counting. Allele frequencies of various genotypes were compared using the χ^2 test. The odds ratio and *P* value were calculated for each allele in the patient and control groups. A *P* value of less than .05 was considered significant with 95% confidence intervals (CI).

Results

Allele Frequency

The alleles for *IL-4*, including C and T alleles at positions –590 and –33, as well as G and T alleles at position –1098, were equally distributed in the patient group. However, there were significant differences in comparison with the controls. The frequency of the T allele at position –33 and the G allele at position –1098 was significantly higher in the patient group (49% in patients vs 28% in controls, *P*<.0001 for position –33; and 49% in patients vs 30% in controls, *P*=.0005 for position –1098). The frequency of the *IL-4RA* G allele in the patient group was also significantly higher than in the control group (23% in patients vs 12% in controls, *P*=.009) (Table 1).

Genotype Frequency

The most frequent genotypes in asthmatic patients were *IL-4* TC at position –590 (100% in patients vs 93% in controls, *P*=.03), *IL-4* TC at position –33 (95% in patients vs 56% in controls, *P*<.0001), and *IL-4* GT at position –1098 (98% in patients vs 59% in controls, *P*=.0001). *IL-4RA* GA at position +1902 in the patient group was significantly overrepresented in comparison with the control group (43% in patients vs 22% in controls, *P*=.004). In contrast, the frequency of the following genotypes in the patient group was significantly lower than in the control group: *IL-4* CC at position –590 (0% in patients vs 7% in controls, *P*=.03), CC at position –33 (3% in patients vs 44% in controls, *P*<.0001), *IL-4* TT at position –1098 (2% in patients vs 40% in controls, *P*=.0001), *IL-4RA* AA at position +1902 (55% in patients vs 77% in controls, *P*=.004) (Table 2).

© 2009 Esmon Publicidad

Table 1. Allele Frequencies of Asthmatic Patients and Controls

Cytokine	Position	Allele	Patients (n=59) N (%)	Controls (n=139) N (%)	*P* Value	Odds Ratio	95% Confidence Interval
IL-4	–590	C	59 (50%)	149 (53.6)	.58	>1	0.73-1.82
		T	59 (50%)	129 (46.4)	.58	<1	0.55-1.36
IL-4	–33	C	60 (50.8%)	200 (71.9)	<.0001	>1	1.55-3.97
		T	58 (49.2%)	78 (28.1)	<.0001	<1	0.25-0.65
IL-4	–1098	G	58 (49.2%)	84 (30.2)	.0005	<1	0.28-0.71
		T	60 (50.8%)	194 (69.8)	.0005	>1	1.40-3.56
IL-4RA	+1902	A	89 (76.7%)	242 (87.7)	.009	>1	1.19-3.92
		G	27 (23.3%)	34 (12.3)	.009	<1	0.25-0.84

Table 2. Genotype Frequencies of Asthmatic Patients and Controls

Cytokine	Position	Genotype	Patients (n=59) N (%)	Controls (n=139) N (%)	*P* Value	Odds Ratio	95% Confidence Interval
IL-4	–590	CC	0 (0%)	10 (7.2)	.03	–	–
		TC	59 (100%)	129 (92.8)	.03	<1	0.00-1.19
		TT	0 (0%)	0 (0)	–	–	–
IL-4	–33	CC	2 (3.4%)	61 (43.9)	<.0001	>1	5.05-137.5
		TC	56 (94.9%)	78 (56.1)	<.0001	<1	0.02-0.24
		TT	1 (1.7%)	0 (0)	.29	<1	0.00-7.38
IL-4	–1098	GG	0 (0%)	1 (0.7)	1.00	–	–
		GT	58 (98.3%)	82 (59)	.0001	<1	0.00-0.17
		TT	1 (1.7%)	56 (40.3)	.0001	>1	5.59-781.9
IL-4RA	+1902	AA	32 (55.2%)	106 (76.8)	.004	>1	1.33-5.44
		GA	25 (43.1%)	30 (21.7)	.004	<1	0.18-0.75
		GG	1 (1.7%)	2 (1.5)	1.00	<1	10.06-23.8

Haplotype Frequency

The frequency of haplotypes of *IL-4* (–1098, –590, –33) in asthmatic patients and healthy controls is shown in Table 3. Each patient had 2 haplotypes. The most frequent haplotype 1 in our patients was *IL-4* TTT, which was not significantly different in comparison with the control group. However, the frequency of *IL-4* TCT in the patient group was significantly greater than in the controls (12.1% in patients vs 0.7% in controls, *P*=.0001). A comparison of haplotype 2 between patients and controls showed that, while the GCC haplotype was the most frequent haplotype in both groups, the GTC haplotype was significantly more common in the patient group (11% in patients vs 0% in controls, *P*=.0001) and the TCC haplotype was significantly less common in this group (0% in patients vs 23% in controls, *P*=.0001).

Asthmatic Phenotypes

Forty-eight cases had mild persistent asthma (81.4%) and the remaining 11 cases had moderate persistent asthma (18.6%). The median serum IgE level of the patients was 62 IU/mL (interquartile range, 16-349 IU/mL). The median FEV_1 was 79.5% (interquartile range, 70%-90%). The skin prick test result was positive to at least 1 allergen in 27 cases (45.8%). House dust mite was the most common allergen in these patients. The frequency of allergens in patients with mild and moderate persistent asthma is presented in Table 4. There were no significant differences in the frequency of allergens between the 2 groups.

There were no significant differences in the mean total serum IgE level between patients with mild persistent and moderate persistent phenotypes (221.59 IU/mL and 174.22 IU/mL,

© 2009 Esmon Publicidad

Table 3. Haplotype Frequencies in Asthmatic Patients and Controls

Haplotype	Patients (n=59) N (%)	Controls (n=139) N (%)	*P* Value	Odds Ratio	95% Confidence Interval
TTC	2 (1.7%)	51 (18.3)	.0001	>1	3.01-78.1
GCC	44 (37.9%)	83 (30)	.18	<1	0.44-1.16
TTT	44 (37.9%)	76 (27.3)	.53	<1	0.52-1.37
TCC	0	65 (23.4)	.0001	–	–
TCT	14 (12.1%)	2 (0.7)	.0001	<1	0.01-0.25
GTT	0	1 (0.3)	1.00	–	–
GCT	1 (0.8%)	0 (0)	.29	<1	0.00-7.36
GTC	13 (11.2%)	0 (0)	.0001	<1	0.00-0.15

Table 4. Skin Prick Test Results in Patients with Mild Persistent and Moderate Persistent Asthma

Allergens	Mild persistent (n=48)	Moderate persistent (n=11)	*P* Value	Total (N=59)
Mite	11 (23%)	2 (18%)	.557	13 (22.0%)
Weeds	4 (8%)	4 (36%)	.031	8 (13.6%)
Trees	5 (10%)	3 (27%)	.154	8 (13.6%)
Grass	4 (8%)	3 (27%)	.108	7 (11.9%)
Cockroach	3 (6%)	1 (9%)	.566	4 (6.8%)
Dander	1 (2%)	1 (9%)	.336	2 (3.4%)
Alternaria	1 (2%)	0	.817	1 (1.7%)

respectively, *P*=.82). For haplotype 1, the mean total serum IgE level in patients with the TTT haplotype was significantly higher than in those with the TCT haplotype (253.0 IU/mL vs 100.8 IU/mL, *P*=.009), whereas for haplotype 2 this level in patients with the GCC haplotype was significantly higher than in patients with the GTC haplotype (254.1 IU/mL vs 103.7 IU/mL, *P*=.006). The mean total serum IgE level in the patients with the TTT/GCC genotype was 258.8 IU/mL, which was significantly higher than the 95.4 IU/mL observed in other genotypes (*P*=.004).

Discussion

Cytokine gene polymorphisms could affect the serum levels of cytokines by influencing transcriptional regulation. While the role of single-nucleotide polymorphisms in some immunological disorders has been reported elsewhere [17-19], the present study was performed to test the association between *IL-4* polymorphisms and asthma. Several authors have recently analyzed the role of genetic factors in asthma, although the results are contradictory [13,14,20-23]. IL-4 is an important cytokine in allergic inflammation and in IgE isotype switching on chromosome 5q31, a linked region in many asthma populations. The results of our study suggested an association between the IL-4 promoter polymorphisms at positions –1098, –590, and –33 and IL-4 RA at position +1902 and asthma, and between the haplotypes of these polymorphisms and total IgE in asthmatic patients. However, we did not find any association between these polymorphisms and asthma severity.

Data on the correlation between T–590C and bronchial asthma are controversial [9,24,25]. Although Rosenwasser et al [26] showed that this polymorphism was associated with elevated levels of IgE in asthmatic families, studies in a white population from Britain, in Australian families, and in Japanese individuals were unable to confirm this result [9,10]. Despite the lack of association between this polymorphism and IgE levels, significantly frequent transmission of the T allele to asthmatic children was found in a Japanese sample, thus suggesting that this polymorphism could be associated with the development of asthma in Japanese individuals, but not through modulating total serum IgE levels [9]. Although there were no significant differences in either the C or T alleles at this position between our asthmatic patients and controls, almost all patients had the TC genotype, which was significantly higher than in the controls. It is possible that single-nucleotide polymorphisms alone lack the power to detect linkage, whereas the haplotype is sufficiently polymorphic to detect a suggestive

 © 2009 Esmon Publicidad

linkage. However, as all patients had the TC genotype at position –590, there was no association between T–590C and asthma severity.

Data on the association between T–33C and asthma are also controversial. Our results showed a strong linkage between T–33C and asthma, a finding that was similar to those of a Russian study [24]. The significantly frequent transmission of the T allele at position –33 in asthmatic patients led to significantly increased frequency of the TC genotype and decreased frequency of the CC genotype. Data on the influence of polymorphisms on the severity of asthma is also controversial. In a British sample, the analysis of disease severity revealed a positive association between both T–33C and T–590C and bronchial hyperresponsiveness [27], whereas our study could not confirm such an association.

As for the influence of G–1098T on a phenotypic manifestation, we found a protective association between bronchial asthma and the IL-4 –1098/G allele, as did a recent study analyzing Macedonian patients [20]. We also found a positive association between the GT genotype and asthma, but no association with the TT genotype, which contrasts with the results of the Macedonian study [20]. These conflicting results could be due to differences in study design and genetic environment.

Analysis of serum IgE levels in association with haplotypes/genotypes indicated that patients with the TTT/GCC genotype have higher levels of IgE; however, there were no significant differences between haplotypes/genotypes and asthma severity. The low number of patients studied is one of the limitations of our study. Studies analyzing additional asthma phenotypes (eg, severe persistent asthma) in larger samples would enable us to test possible associations between the genetic promoter polymorphisms for *IL-4* and the asthma phenotype.

In conclusion, analysis of the polymorphisms of the *IL-4* gene promoter revealed a strong association between these polymorphisms and bronchial asthma. An association between their haplotypes and serum total IgE was also found. Our results highlight the value of allele frequency and of the association between polymorphisms and their phenotypic manifestations, which are highly variable according to population.

Acknowledgments

This study was supported in part by a grant from the Immunology, Asthma and Allergy Research Institute and Tehran University of Medical Sciences, Tehran, Iran.

References

1. Boushey HA, Holtzman MJ, Sheller JR, Nadel JA. Bronchial hyperreactivity. Am Rev Respir Dis. 1980;121:389-413.
2. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med. 1989;320:271-77.
3. Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. N Engl J Med. 1981;305:1551-9.
4. Hopp RJ, Townley RG, Biven RE, Bewtra AK, Nair NM. The presence of airway reactivity before the development of asthma. Am Rev Respir Dis. 1990;141:2-8.
5. Postma DS, Bleecker ER, Amelung PJ, Holroyd KJ, Xu J, Panhuysen CI, Meyers DA, Levitt RC. Genetic susceptibility to asthma—bronchial hyperresponsiveness coinherited with a major gene for atopy. N Engl J Med. 1995;333:894-900.
6. Xu J, Postma DS, Howard TD, Koppelman GH, Zheng SL, Stine OC, Bleecker ER, Meyers DA. Major genes regulating total serum immunoglobulin E levels in families with asthma. Am J Hum Genet. 2000;67:1163-73.
7. Coleman JW, Holliday MR, Kimber I, Zsebo KM, Galli SJ. Regulation of mouse peritoneal mast cell secretory function by stem cell factor, IL-3 or IL-4. J Immunol. 1993;150:556-62.
8. Kawashima T, Noguchi E, Arinami T, Arinami T, Yamakawa-Kobayashi K, Nakagawa H, Otsuka F, Hamaguchi H. Linkage and association of an interleukin 4 gene polymorphism with atopic dermatitis in Japanese families. J Med Genet. 1998;35:502-4.
9. Noguchi E, Shibasaki M, Arinami T, Takeda K, Yokouchi Y, Kawashima T. Association of asthma and the interleukin- 4 promoter gene in Japanese. Clin Exp Allergy. 1998;28:449-53.
10. Walley AJ, Cookson WOCM. Investigation of an interleukin-4 promoter polymorphism for associations with asthma and atopy. J Med Genet. 1996;33:689-92.
11. Basehore MJ, Howard TD, Lange LA, Moore WC, Hawkins GA, Marshik PL, Harkins MS, Meyers DA, Bleecker ER. A comprehensive evaluation of IL4 variants in ethnically diverse populations: association of total serum IgE levels and asthma in white subjects. J Allergy Clin Immunol. 2004;114:80-7.
12. Collaborative Study on the Genetics of Asthma. A genome-wide search for asthma susceptibility loci in ethnically diverse populations. Nat Genet. 1997;15:389-92.
13. Movahedi M, Mahdaviani SA, Rezaei N, Moradi B, Dorkhosh S, Amirzargar AA IL-10, TGF-beta, IL-2, IL-12, and IFN-gamma cytokine gene polymorphisms in asthma. J Asthma. 2008;45(9):790-4.
14. Mahdaviani SA, Rezaei N, Moradi S, Dorkhosh S, Amirzargar A.A, Movahedi M. Proinflammatory cytokine gene polymorphisms among Iranian patients with asthma. J Clin Immunol. 2009;29(1):57-62.
15. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007.1. J Allergy Clin Immunol. 2007;120(Suppl 5):94-138.
16. Amirzargar AA, Naroueynejad M, Khosravi F, Dianat S, Rezaei N, Mytilineos J, Nikbin B. Cytokine single nucleotide polymorphisms in Iranian populations. Eur Cytokine Netw. 2008;19:104-12.
17. Amirzargar AA, Bagheri M, Ghavamzadeh A, Alimoghadam K, Khosravi F, Rezaei N, Moheydin M, Ansaripour B, Moradi B, Nikbin B. Cytokine gene polymorphism in Iranian patients with chronic myelogenous leukaemia. Int J Immunogenet. 2005;32:167-71.
18. Amirzargar AA, Rezaei N, Jabbari H, Danesh AA, Khosravi F, Hajabdolbaghi M, Yalda A, Nikbin B. Cytokine single nucleotide polymorphisms in Iranian patients with pulmonary tuberculosis. Eur Cytokine Netw. 2006;17:84-9.
19. Rezaei N, Amirzargar AA, Shakiba Y, Mahmoudi M, Moradi B, Aghamohammadi A. Proinflammatory cytokine gene single nucleotide polymorphisms in common variable immunodeficiency. Clin Exp Immunol. 2009;155(1):21-7.

© 2009 Esmon Publicidad

20. Trajkov D, Mirkovska-Stojkovikj J, Arsov T, Petlichkovski A, Strezova A, Mladenovska OE, Sandevska E, Gogusev J, Spiroski M. Association of cytokine gene polymorphisms with bronchial asthma in Macedonians. Iran J Allergy Asthma Immunol. 2008;7:143-56.
21. McLeish S, Turner SW. Gene–environment interactions in asthma. Arch Dis Child. 2007;92;1032-5.
22. Hosseini-Farahabadi S, Tavakkol-Afshari J, Rafatpanah H, Farid Hosseini R, Khaje Daluei M. Association between the polymorphisms of IL-4 gene promoter (-590C>T), IL-13 coding region (R130Q) and IL-16 gene promoter (-295T>C) and allergic asthma. Iran J Allergy Asthma Immunol. 2007;6(1):9-14.
23. Nadi E, Hajilooi M, Zeraati F, Ansari M, Tavana S, Hashemi SH, Rafiei A. E-selectin S128R polymorphism leads to severe asthma. Iran J Allergy Asthma Immunol. 2007;6:49-57.
24. Gervaziev YV, Kaznacheev VA, Gervazieva VB. Allelic polymorphisms in the interleukin-4 promoter regions and their association with bronchial asthma among the Russian population. Int Arch Allergy Immunol. 2006;141:257-64
25. Kabesch M, Tzotcheva I, Carr D, Höfler C, Weiland SK, Fritzsch C, von Mutius E, Martinez FD. A complete screening of the IL4 gene: novel polymorphisms and their association with asthma and IgE in childhood. J Allergy Clin Immunol. 2003;112:893-8.
26. Rosenwasser LJ, Klemm DJ, Dresback JK, Inamura H, Mascali JJ, Klinnert M, Borish L. Promoter polymorphisms in the chromosome 5 gene cluster in asthma and atopy. Clin Exp Allergy. 1995;25:74-8.
27. Beghe B, Barton S, Rorke S, Peng Q, Sayers I, Gaunt T, Keith TP, Clough JB, Holgate ST, Holloway JW. Polymorphisms in the interleukin-4 and interleukin-4 receptor alpha chain genes confer susceptibility to asthma and atopy in a Caucasian population. Clin Exp Allergy. 2003;33:1111-7.

Manuscript received December 7, 2008; accepted for publication February 20, 2009.

Seyed Alireza Mahdaviani, MD

Department of Allergy and Clinical Immunology
Children's Medical Center Hospital
62 Qarib St, Keshavarz Bkvd
Tehran 14194, Iran
E-mail: mahdavini@yahoo.com

© 2009 Esmon Publicidad