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ORIGINAL ARTICLE

Polymorphisms of the CD14 gene and atopic phenotypes in Czech patients with IgE-mediated allergy

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Abstract IgE-mediated allergy is a common chronic disorder resulting from interactions between genetic and environmental factors. The gene encoding CD14 is a positional candidate gene for allergic diseases as it is localised on chromosome 5q31.1, a region linked to asthma and bronchial hyperresponsiveness. We investigated the relationship among atopic phenotypes and six polymorphisms in the CD14 gene. Polymerase chain reaction with RFLP analyses was used to determine the CD14 genotypes in subjects with IgE-mediated allergic diseases (n=282) and random controls (n=187). No significant differences in allele or genotype frequencies for individual polymorphisms between patients and controls were found. However, when atopic patients were subdivided into subjects with positive and with negative skin prick tests for separate antigens, T allele of the 1341G/T polymorphism was significantly associated with positive reactivity to mites (P=0.007) and moulds (P=0.041). Similarly, the C allele frequency of the –159C/T variant was increased in patients with positive skin prick tests for mites (P=0.046) and moulds (P=0.056). In haplotype analysis, the common –1619A/–1359G/–550C/–159C/+1188G/+1341T haplotype was associated with positive reaction to these antigens (P values: 0.0008–0.0035). Our study supports the idea that CD14 plays a role in IgE-mediated allergic diseases, and its gene polymorphisms can be important for manifestation of these disorders.

Keywords Allergic diseases · Asthma · Polymorphism · Gene · SNP · CD14

Introduction

Epidemiological studies have shown a worldwide increase in the prevalence of asthma and other allergic diseases in recent decades (Keller and Lowenstein 2002). It is evident that IgE-mediated allergy is the result of complex interactions between genetic predisposition and multiple environmental influences (Marks 2006). Linkage studies have indicated that one or more loci on chromosome 5q may control total IgE as well as asthma and bronchial hyperresponsiveness to nonspecific stimuli (Moffatt and Cookson 1999). The gene encoding CD14 is localised on chromosome 5q31.1, and it is just one of many genes that appear to contribute to the expression of the allergic phenotype. Cluster differentiation antigen (CD14), a 55-kD glycoprotein, is a pattern-recognition factor that plays a central role in innate immunity through recognition of bacterial lipoglycans (LPS). According to Vercelli et al. (2001a), exposure to bacterial products, such as LPS, may modulate IgE regulation, possibly by activating innate immune pathways that promote Th1 differentiation and/or suppress Th2-dependent IgE responses.

CD14 protein exists as a membrane-bound molecule (mCD14), expressed primarily on the surface of monocytes/macrofages, dendritic cells and neutrophils (Haziot et al. 1988), and as a soluble form (sCD14) in serum. Binding of LPS to sCD14 entails activation of signalling via Toll-like receptor 4 (TLR4) in antigen-presenting cells (APC) and subsequent secretion of IL-12 from these cells (Baldini et al. 2002).

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A promoter polymorphism C(–159)T (also known as –260C/T) in the CD14 gene has been found to be associated with elevated levels of soluble CD14 (Baldini et al. 1999; Kabesch et al. 2004), and inversely associated with levels of total serum IgE (Baldini et al. 1999; Leung et al. 2003). Koppelman et al. (2001) reported an association of CC homozygotes of this polymorphism with higher numbers of positive skin prick tests compared to CT and TT genotypes. Recently, several single nucleotide polymorphisms (e.g. at positions –1,619, –1,359, –1,145, –809, and –550) were characterised in the promoter of the gene encoding CD14. Vercelli et al. (2001b) and Tan et al. (2006) showed that carriers of the –1359T/–1145A/–159C haplotype had the highest levels of IgE, and the lowest levels of sCD14, and conversely carriers of the 1359G/–1145G/–159T haplotype had the highest levels of sCD14 and the lowest IgE values. According to Martin et al. (2006), during acute asthma, plasma sCD14 levels were higher, but increases were only in subjects with CD14 –159TT and –159CT, and not in those with –159CC. However, five single nucleotide polymorphisms (1188G/C, 1307A/T, 1335C/G, 1341G/T and 1344G/C) were detected also in exon 2 of the CD14 gene (Hayden et al. 2000; Riva 2001–2004).

The aim of this case-control study was to investigate an association of the six polymorphisms in the promoter region (at positions –1,619, –1,359, –550, and –159) and in exon 2 of the CD14 gene (at positions 1,188, and 1,341) with phenotypes of IgE-mediated allergic diseases in the Czech, highly homogeneous population.

Materials and methods

Characteristics of subjects

Caucasian subjects of exclusively Czech nationality (n=469) were included in this study. All subjects were selected using a detailed questionnaire modified from the American Thoracic Society respiratory questionnaire (American Thoracic Society 1988) regarding lifetime symptoms suggestive of asthma, rhinitis and atopic dermatitis, extended with additional questions on symptoms and therapy as well as on other diseases. Phenotype status was assigned without previous knowledge of genotypes by two investigators independently.

A total of 282 patients with clinically manifested IgE-mediated asthma and/or rhinitis, 143 men and 139 women, aged 25.1±10.8 years (mean±SD) were studied. A total of 187 reference age– and gender-selected subjects (83 men and 104 women), aged 29.9±8.7 years, who were free of lung, skin and cardiovascular disease and had no clinical evidence of personal or familial allergic diseases, asthma, hay fever or eczema, were recruited as controls.

Asthma was defined by using the questionnaire together with a physician's diagnosis of asthma, according to the Global Initiative on Asthma (GINA) criteria (Global Strategy for Asthma Management and Prevention, Global Initiative For Asthma 2002). IgE-mediated allergic disease was recognised by total IgE (>180 IU/ml), specific IgE (>0.35 kU/l) and/or a positive skin prick test to one or more allergens (e.g. common grass, tree pollen mixtures, house dust mites, common moulds) as described previously (Buckova et al. 2002).

All the subjects, or their parents in case of children, gave written informed consent for participation in the study. The study was approved by the Committee for the Ethics of Medical Experiment on Human Subjects, Medical Faculty, Masaryk University Brno.

Genotype identification

Genomic DNA was isolated from peripheral blood leukocytes by a standard method using the proteinase K digestion of cells. Genotyping of the –159C/T and –1359G/T variants was performed by the PCR–RFLP methods as described previously (Buckova et al. 2003).

Detection of the bi-allelic polymorphism 1188C/G in the exon of the CD14 gene

The 1188C/G polymorphism was detected by a newly developed PCR method and a subsequent restriction analysis with BsrBI endonuclease (New England Biolabs). Specific primer sequences (5′-GGGTGTGGGAACCCTGGTGCC-3′ and 5′-AAGATTTTAATAAAGGTGGGGCAAAG-3′) were derived from the original sequence (GenBank, accession no. X74984). The PCR was performed in a final volume of 15 μl, containing 50 mmol KCl, 10 mM Tris–HCl buffer (pH 8.4), 3.0 mM $MgCl_2$, 3 pM each primer, 300 μM dNTP and 0.1 μg of genomic DNA in the presence of 0.1 U of Taq polymerase (MBI Fermentas) to provide 163-bp products. After the initial denaturation step (95°C for 6 min), each cycle (an additional 30 ones) consisted of 95°C denaturation for 30 s, 60°C annealing for 15 s, 72°C extension for 15 s, with the final extension lasting for 10 min at 72°C. The 12 μl of the PCR product was digested with BsrBI for 2 h at 37°C. The digestion revealed fragments of 146- and 19-bp lengths for the G allele, and 165-bp for the C allele.

Detection of the bi-allelic polymorphism 1341G/T in the exon of the CD14 gene

The 1341G/T polymorphism was detected by a newly developed PCR method and a subsequent restriction analysis with AgeI endonuclease (New England Biolabs). Specific primer sequences (5′-ACCTTTATTAAATCTTAAACACCGGTTC-3′ and 5′-GACAGATAGGGTTTCTTAGGGAGTTAG-3′) were derived from the original sequence (GenBank, accession no. X74984). The PCR was performed in a final volume of 15 μl, containing 50 mmol KCl, 10 mM Tris–HCl buffer (pH 8.4), 1.7 mM $MgCl_2$, 5 pM each primer, 300 μM dNTP and 0.1 μg of genomic DNA in the presence of 0.1 U of Taq polymerase (MBI Fermentas) to provide 150-bp products. After the initial denaturation step (95°C for 5 min), each cycle (anadditional 35) consisted of 95°C denaturation for 30 s, 59°C annealing for 15 s, 72°C extension for 20 s, with the final extension lasting for 10 min at 72°C. The 12 μl of the PCR product was digested with AgeI for 4 h at 37°C. The digestion revealed fragments of 128- and 22-bp lengths for the T allele, and 150-bp for the G allele.

Detection of the –1619 A/G polymorphism in the promoter of the CD14 gene

The –1619A/G polymorphism was detected by a newly developed PCR method and a subsequent restriction analysis with BccI endonuclease (New England Biolabs). Specific primer sequences (5′-CCCATCTCTAC TAAAAATACAAAATTAGCC-3′ and 5′-CACACC CGGCCTGAAAGTCTTTTGTA-3′) were derived from the original sequence (GenBank, accession no. X74984). The PCR was performed in a final volume of 15 μl, containing 50 mmol KCl, 10 mM Tris–HCl buffer (pH 8.4), 1.5 mM $MgCl_2$, 8 pM each primer, 300 μM dNTP and 0.2 μg of genomic DNA in the presence of 0.5 U of Taq polymerase (MBI Fermentas) to provide 208-bp products. After the initial denaturation step (95°C for 3 min), each cycle (an additional 30) consisted of 95°C denaturation for 30 s, 61°C annealing for 20 s, 72°C extension for 20 s, with the final extension lasting for 7 min at 72°C. The 12 μl of the PCR product was digested with RsaI for 4 h at 37°C. The digestion revealed fragments of 183- and 25-bp lengths for the G allele, and 208-bp for the A allele.

Detection of the –550 C/T polymorphism in the promoter of the CD14 gene

The –550C/T polymorphism was detected by a newly developed PCR method and a subsequent restriction analysis with RsaI endonuclease (New England Biolabs). Specific primer sequences (5′-GAGATCATG GCACTCTACTCCAG-3′ and 5′-GAATTAGGTTC AAGAAAAGGAAGAT-3′) were derived from the original sequence (GenBank, accession no. X74984). The PCR was performed in a final volume of 15 μl, containing 50 mmol KCl, 10 mM Tris–HCl buffer (pH 8.4), 2.5 mM $MgCl_2$, 5 pM each primer, 300 μM dNTP and 0.2 μg of genomic DNA in the presence of 0.5 U of Taq polymerase (MBI Fermentas) to provide 161-bp products. After the initial denaturation step (95°C for 6 min), each cycle (an additional 35) consisted of 95°C denaturation for 30 s, 59°C annealing for 15 s, 72°C extension for 20 s, with the final extension lasting for 10 min at 72°C. The 12 μl of the PCR product was digested with BccI for 4 h at 37°C. The digestion revealed fragments of 143- and 18-bp lengths for the C allele, and 161-bp for the T allele.

Statistics

All statistical analyses were performed using the programme package Statistica v. 6.0 (StatSoft, Tulsa, OK, USA). χ^2-test was used to test for deviation of genotype distribution from HWE and for comparison of differences in genotype frequencies among groups. Differences in allele frequencies of polymorphisms fulfilling HWE expectation were tested by a two-tail Fisher exact test. $P<0.05$ was considered statistically significant. Testing of allele or genotype frequencies for several polymorphisms among the three groups involves multiple comparisons; therefore necessary corrections had to be applied. Where appropriate, Bonferroni correction was used to adjust the α level according to the number of independent comparisons to the overall value of 0.05. Adjusted P values for particular analyses are denoted as P_{corr}. Haplotype frequencies were calculated from the observed genotype frequencies assuming that during zygote formation, haplotypes combine at random according to their frequencies in the set (the assumption being analogous to Hardy–Weinberg equilibrium). This assumption was verified by a reversed calculation of the expected genotype frequencies from the calculated haplotype frequencies. Differences between the two groups (patients and controls) were tested by a simulation using the Monte Carlo method. In this test, 10,000 random simulations were performed to generate tables having the same marginal totals as the observed data, and the number of occurrences of the χ^2 value greater than or equal to the χ^2 value associated with the real table was counted.

Results

The genotype distributions for all polymorphisms were consistent with Hardy–Weinberg equilibrium in both allergic and control groups, except disequilibrium of –1619A/G polymorphism in atopic patients. There was a similar proportion of males/females among allergic patients as in the control group.

No significant differences between the allergic patients and the healthy controls were found in the genotype or allelic frequencies for the six investigated polymorphisms of the CD14 gene (Table 1).

However, when the patients were subdivided into those with positive and those with negative skin prick tests for separate antigens, the CD14 1341G/T polymorphism was significantly associated with reactivity to the mites and marginally to the moulds (Table 2). Patients with IgE-mediated asthma and/or rhinitis and positive prick test for these antigens were more often carriers of the T allele of the CD14 1341G/T polymorphism (P=0.007, P_{corr}<0.05 for mites; P=0.041, P_{corr}>0.05 for moulds). Similarly, the C allele of the –159C/T (also known as –260) variant was less significantly associated with these antigens (P=0.046, P_{corr}>0.05 for mites and P=0.056, P_{corr}>0.05 for moulds).

Furthermore, we performed a haplotype analysis using the Monte Carlo method. The frequencies of all observed haplotypes of the CD14 gene are summarised in Table 4. We found only five major haplotype combinations with a frequency of more than 5% because all six variants in the CD14 gene were in linkage disequilibrium with each other to various degrees (Table 3). Although we did not find significant differences in the frequency of haplotype combinations between allergic versus control subjects (Table 4), the common haplotype 5 (–1619A/–1359G/–550C/–159C/+1188G/+1341T) was associated with positive reaction to the mite and mould antigens (P values from 0.0008–0.0035, see Table 5). In addition, haplotype 2 (–1619A/–1359G/–550C/–159T/+1188G/+1341G) was protective; it was present only rarely in patients with positive reaction to the mould (P=0.018, P_{corr}<0.05). Haplotype 3 (–1619G/–1359G/–550C/–159T/+1188G/+1341G) was similarly protective against mites (P=0.037, P_{corr}>0.05).

Finally, there were no significant associations among the CD14 alleles and/or genotypes and/or haplotypes and several quantitative traits investigated in our study, including total IgE levels, selected specific IgE levels or pulmonary function tests, except marginal association of the CD14 –1359G/T variant with total IgE levels (165.4±307.1 IU/ml in GG + GT genotypes vs. 317.3±317.6 IU/ml in TT homozygotes, P=0.026, P_{corr}>0.05).

Discussion

Allergic predisposition is regarded as a multifactorial condition whose onset and severity are influenced by both genetic and environmental factors. These diseases are generally characterised by the presence of elevated

Table 1 Genotype and allele frequencies of the CD14 polymorphisms in both groups

Controls (n=187)					Atopic patients (n=282)				
–1619A/G									
AA	AG	GG	A (%)	G (%)	AA	AG	GG	A (%)	G (%)
59	100	28	58.3	41.7	92	151	39	59.4	40.6
–1359G/T									
GG	GT	TT	G (%)	T (%)	GG	GT	TT	G (%)	T (%)
111	64	12	76.5	23.5	178	94	10	79.8	20.2
–550C/T									
CC	CT	TT	C (%)	T (%)	CC	CT	TT	C (%)	T (%)
105	72	10	75.4	24.6	171	98	13	78.0	22.0
–159C/T									
CC	CT	TT	C (%)	T (%)	CC	CT	TT	C (%)	T (%)
51	97	39	53.2	46.8	78	146	58	53.5	46.5
+1188C/G									
CC	CG	GG	C (%)	G (%)	CC	CG	GG	C (%)	G (%)
4	44	139	13.9	86.1	6	71	205	14.7	85.3
+1341G/T									
GG	GT	TT	G (%)	T (%)	GG	GT	TT	G (%)	T (%)
92	80	15	70.6	29.4	124	130	28	67.0	33.0

Comparisons performed by means of two-tail Fisher-exact test (for alleles); for genotype frequencies χ^2 -test was used

P=NS in all comparisons. Bonferroni corrected P value (P_{corr}) for single test (12 independent comparisons) equals 0.004

Table 2 Results of the analysis of genetic data in relation to the atopic phenotype

Gene variant: prick test for mites				
+1341 G/T	GG (%)	GT (%)	TT (%)	*P* value[a]
Negative test	67 (47.9)	63 (45.0)	10 (7.1)	0.007
Positive test	28 (32.2)	44 (50.6)	15 (20.7)	
–159 C/T	CC (%)	CT (%)	TT (%)	
Negative test	32 (22.9)	77 (55.0)	31 (22.1)	0.046
Positive test	33 (37.9)	39 (44.8)	15 (17.2)	
–1619 A/G	AA (%)	AG (%)	GG (%)	
Negative test	38 (27.1)	81 (57.9)	21 (15.0)	0.042
Positive test	39 (44.8)	37 (42.5)	11 (12.6)	
Gene variant: prick test for moulds				
+1341 G/T	GG (%)	GT (%)	TT (%)	
Negative test	60 (43.5)	68 (49.3)	10 (7.2)	0.041
Positive test	19 (29.7)	35 (54.7)	10 (15.6)	
–159 C/T	CC (%)	CT (%)	TT (%)	
Negative test	32 (25.2)	68 (53.5)	27 (21.3)	0.056
Positive test	22 (35.5)	34 (54.8)	6 (9.7)	

[a] Statistical significance for the comparison of allele frequencies (Fisher exact test)

Table 3 Pairwise linkage disequilibrium (LD) for all possible 2-way comparisons among six polymorphisms in the CD14 gene in control and atopic groups

	SNP1 –1619	SNP2 –1359	SNP3 –550	SNP4 –159	SNP5 +1188	SNP6 +1341
SNP1 controls		1.00	0.88	1.00	1.00	1.00
Atopics		0.88	0.61	1.00	0.95	1.00
SNP2 controls			0.89	1.00	1.00	0.93
Atopics			0.85	0.91	1.00	1.00
SNP3 controls				0.86	1.00	1.00
Atopics				0.65	0.77	0.91
SNP4 controls					1.00	1.00
Atopics					0.96	1.00
SNP5 controls						0.97
Atopics						0.98

LD was measured by Lewontin standardised disequilibrium coefficient |D′|

plasma levels of IgE and Th2-type cytokines. Major genetic susceptibility locus on chromosome 5 has been identified by genome-wide screening (Ober et al. 2000). CD14 is one of the many genes of this region, and our study represents an investigation into the role of this gene in IgE-mediated allergic diseases in the Czech population.

First, we looked for a possible difference in the allele and genotype frequencies of six polymorphisms in the promoter and in exon 2 of the CD14 gene between healthy and allergic subjects. Because these frequencies did not differ between the two groups, this gene does not seem to constitute, per se, a risk for the development of the IgE-mediated allergic diseases.

Secondly, we detected the associations of the T allele of the 1341G/T exon polymorphism and less significantly the C allele of the –159C/T promoter variant with the positive skin prick tests to the mites and to the moulds. This is in accordance with our previous study, where we found the associations of C allele of the C(–159)T promoter polymorphism in the CD14 gene with the positive skin prick test to the moulds in the Czech population (Buckova et al. 2003). In addition, Koppelman et al. (2001) have reported a

Table 4 Haplotype frequency estimation for the atopic and control populations

	–1619A/G	–1359G/T	–550C/T	–159C/T	1188C/G	1341G/T	Atopic patients	Controls
	A	G	C	C	C	G	0.000000	0.002674
	A	G	C	T	C	G	0.000000	0.002674
	G	G	T	T	C	G	0.001898	0.000000
	A	G	C	C	G	G	0.005584	0.000000
	A	T	C	C	G	G	0.018382	0.016416
	A	G	T	C	G	G	0.003332	0.002683
HAP 1	A	T	T	C	G	G	0.178375	0.216195
HAP 2	A	G	C	T	G	G	0.053411	0.047723
HAP 3	G	G	C	T	G	G	0.373323	0.397723
	G	T	C	T	G	G	0.005370	0.000000
	A	G	T	T	G	G	0.005099	0.000405
	G	G	T	T	G	G	0.025437	0.019390
HAP 4	A	G	C	C	C	T	0.142856	0.126374
	A	G	T	C	C	T	0.002409	0.007316
HAP 5	A	G	C	C	G	T	0.181215	0.157744
	A	T	C	C	G	T	0.000000	0.002683
	A	G	T	C	G	T	0.003307	0.000000

higher number of positive skin tests in C(–159) homozygotes in a population from the Netherlands. Other association studies investigating polymorphisms in exons of the CD14 gene have not been published so far.

Since it has been suggested that haplotype analyses may be more informative for determining associations between phenotypes and genetic variation than SNPs, we also performed haplotype analyses using the Monte Carlo method, which offers better biological assessment of gene variability. We found that some of the common haplotypes were associated with intermediary phenotypes of allergic diseases, such as positivity (or negativity) of the skin prick test to several antigens.

Table 5 Results of the haplotype frequency estimation for the atopic subgroup according to prick test positivity/negativity

	Negative	Positive	*P* value[a]
HAP 5			
Prick test: mites			
Negative	87	39	0.0035
Positive	37	41	
Prick test: moulds			
Negative	81	36	0.0008
Positive	23	33	
HAP 3			
Prick test: mites			
Negative	35	91	0.0366
Positive	34	45	
Prick test: moulds			
Negative	37	80	NS
Positive	22	34	
HAP 2			
Prick test: mites			
Negative	112	14	NS
Positive	72	6	
Prick test: moulds			
Negative	101	16	0.0179
Positive	55	1	

[a] Statistical significance for the comparison of allele frequencies (Fisher exact test). *NS* Non-significant value

CD14 is a multifunctional receptor and may play a role in different biological and pathophysiological processes: apoptosis, sepsis, and inflammatory diseases, such as atherosclerosis and allergic diseases (Shimada et al. 2000; Baldini et al. 2002). There are several plausible explanations for a possible role of CD14 in IgE-mediated allergic diseases. CD14 functions as a receptor for LPS on several types of cells, thereby inducing mediator and cytokine release (Gao et al. 1999). Complexes of CD14 and bacterial LPS may increase Th1-favoured T cell differentiation and activate greater expression of sCD14, which may result in a reduction in the serum IgE levels (Kusunoki et al. 2002). In addition, bronchoalveolar lavage studies suggest that CD14-mediated cell activation could play a role in the inflammatory response after allergen challenge (Dubin et al. 1996).

The results of previous studies indicate that the CD14 gene plays an important role in the determination of sensitisation to environmental allergens as well as in innate immunity against pathogens (Tan et al. 2006). The results of association studies of the CD14 gene with atopic phenotype in our populations confirm the importance of not only promoter, but also exon polymorphisms in the CD14 gene in modulating expression and severity of the atopic diseases. On the basis of our results, it seems unlikely that the association of CD14 with atopic diseases and related traits is caused by only one polymorphism. More probably, the haplotype combinations of several polymorphisms may

be involved in the protection against or susceptibility to these diseases.

However, because differences in the genetic background influence allele frequencies of phenotype-associated genes, more studies in other ethnic populations should be undertaken in order to analyse the putative relevance of the CD14 gene in IgE-mediated allergy.

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