



Haplotype analysis of the *interleukin-18* gene in Czech patients with allergic disorders

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ABSTRACT

The *interleukin-18* (*IL-18*) gene on chromosome 11q22 has been suggested as a susceptibility factor for allergies. To test for a possible role of *IL-18* polymorphisms in Czech population, case-control study including 958 subjects (633 allergic patients and 325 healthy controls) was performed. An allele-specific polymerase chain reaction was used to analyze variants at positions –607 C/A (rs1946518) and –137 G/C (rs187238) in the promoter region together with the polymerase chain reaction–restriction fragment length polymorphism method for the detection of polymorphism at position –140 C/G (previously –133 C/G, rs360721) in intron 1 of the *IL-18* gene. The –1297 C/T (rs360719) polymorphism was genotyped by real-time–polymerase chain reaction, using a predevelopment TaqMan allele discrimination assay. There were no significant differences in distribution of alleles or genotypes in any of four single nucleotide polymorphisms in the *IL-18* gene between controls and patients. However, subsequent analysis revealed a significant difference in haplotype frequencies between the allergic patients and healthy subjects ($p < 0.01$). Haplotype formed by –1297 C/–607 A/–137 C/–140 C alleles occurred significantly more frequently in patients than controls (0.0433 vs 0.0129; $p < 0.0003$; $p_{\text{corr}} < 0.01$, OR = 3.37; 95% CI = 1.59–7.14). In contrast, there was no relationship among the *IL-18* variants and total serum IgE level. Our results indicate that promoter polymorphisms in the *IL-18* gene act in interaction and could play a role in allergic disorders.

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1. Introduction

Allergic diseases, such as asthma, allergic rhinitis, and atopic eczema/dermatitis syndrome (AEDS) are one of the major causes of morbidity in different countries [1]. Genes and environmental factors are both known to play a role in the rising incidence of allergic diseases over the past decades. The increasing incidence of allergic diseases in recent decades outlines the importance of environmental factors in the risk assessment [2]. However, strong genetic components associated with asthma and other clinical manifestations of allergies have been supported by family and twin studies [3], and many genes have been identified or suspected to be involved in the pathogenesis of allergic diseases [4]. Interleukin-18 (*IL-18*) is among the possible factors that can play a role in the development of allergies. It is a pro-inflammatory cytokine, a member of the IL-1 family that was originally described as interferon- γ (INF- γ)–inducing factor. It is generally considered to be involved in

the T helper type 1 (T_H1)–mediated immune response; it also inhibits IgE synthesis, usually by acting synergistically with IL-12. By contrast, IL-18 might initiate T_H2 responses with production of IgE via the stimulation of IL-4 and IL-13 synthesis in mast cells and in basophil and eosinophil recruitment, such as allergic inflammation [5]. The increased IL-18 levels in the nasal secretions from allergic rhinitis (AR) patients were observed to be significantly higher than those of controls [6]. In addition, IL-18 concentrations in the sera from patients with asthma (AB) [7–9] and AEDS [9–11] are consistently elevated compared with those in healthy subjects.

The gene for human *IL-18* is located on chromosome 11q22.2–22.3, a region that has been previously linked to atopy-related traits [12,13]. It is composed of six exons [14], and several polymorphisms have been identified in the *IL-18* gene. Among them, –607 A/C (rs1946518), –137 C/G (rs187238) in the promoter region, and –140 C/G (previously –133 C/G, rs4988359) in intron 1 have been studied in detail with respect to etiopathogenesis of allergic diseases [15–18] and transcriptional activity or IL-18 production by monocytes [19–21]. Current results have indicated the in-

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consistent association between *IL-18* gene variants and clinical/intermediary phenotypes of allergy in different populations [15–18,22–31]. However, a novel putative functional variant –1297 C/T (rs360719) within the *IL-18* promoter region that seems to have an important role in *IL-18* expression was recently associated with susceptibility to SLE [32]. Its role in allergic disorders, however, is still unknown.

On the basis of previous findings, we evaluated four single nucleotide polymorphisms (SNPs) in the *IL-18* gene in groups of healthy and allergic Czech subjects, with two major goals: (1) to investigate a possible association of selected variants and their combinations (i.e., haplotypes) with susceptibility to allergic diseases; and (2) to analyze their associations with different allergic/asthmatic phenotypes.

2. Subjects and methods

2.1. Subjects

This population-based, case-control study comprised 958 unrelated Czech subjects living in the South Moravia region. All subjects completed a detailed questionnaire considering lifetime symptoms suggestive of asthma, rhinoconjunctivitis, and AEDS, which was extended with additional questions regarding symptoms and therapy for other diseases. A total of 633 patients with clinically manifest allergic diseases (312 men and 321 women, aged 32.6 ± 13.0 years [mean $\pm$ SD]) were studied. Asthma diagnosis was based on the following criteria: (a) current diagnosis of asthma according to the physician's record, (b) symptoms, and (c) use of antiasthma medication. The diagnosis and classification of the clinical severity of asthma was established according to the Global Initiative for Asthma guidelines (GINA) [33]. The diagnosis of allergic rhinitis was based on coordination between a typical history of allergic symptoms of either perennial or seasonal rhinitis and a diagnostic test for IgE-mediated allergy [34]. The AEDS was defined according to the diagnostic criteria for atopic eczema initially proposed by Hanifin and Rajka [35]. Atopy was defined as the presence of positive skin test reaction (≥ 3 mm greater than reaction to saline) to one or more of the common allergens (house dust mite, common mixed grass and tree pollens, mixed molds, cat and dog dander, together with histamine and normal saline as a positive and negative control), and/or raised specific serum IgE levels (>0.35 kU/l by AlaSTAT test (DPC Biermann, Bad Nauheim, Germany) produced in response to one or more of the common allergens, including *Der-matophagoides farinae*, grass pollens, animal danders, and molds) and/or raised total serum IgE levels above normal values (>100 IU/ml in nonsmoking adults measured by the nephelometric test (Dade-Behring, Mannheim, Germany) as described previously [36].

The control group consisted of 325 healthy subjects (167 men and 158 women), aged 37.25 ± 16.0 years, who met the following criteria: (a) no prior or current diagnosis of asthma and/or rhinitis and/or dermatitis, (b) no history of wheezing, shortness of breath and other symptoms of allergic diseases, (c) no use of antiasthma medications, and (d) no parental history of atopic diseases.

The study was approved by the Committee for Ethics of the Medical Faculty, Masaryk University Brno, and informed consent was obtained from all participants, in line with the Declaration of Helsinki, before inclusion in the study.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood leukocytes by a standard method using the proteinase K digestion of cells. For detection of SNPs in promoter regions at positions –607 C/A and –137 C/G, allele-specific PCR according to Giedraitis et al. [37] was used with slight adaptations. The original PCR-RFLP method according to Kruse et al. was used for the analysis of SNP in intron 1 at

position –140 C/G (previously –133 C/G) [15]. The PCR products were then digested by the restriction enzyme SmaI. The genotyping of –1297 C/T (rs 360719) polymorphism was performed using a predevelopment TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA) according to Sanchez et al. [32]. The genotyping was performed by one investigator who was unaware of the phenotype. Of the subjects, 10% were genotyped twice for each polymorphism to verify correctness of the analysis.

2.3. Statistical analysis

The power of study to detect significant differences between study groups was calculated according to Whitley and Ball [38] and Altman [39]. Considering minor allele frequencies and our sample size, and odds ratio (OR) of 1.5 could be detected with a power of 0.75–0.80 and a significance level of 0.05. This shows that our sample size was large enough to detect the association with an acceptable level of significance.

Comparisons were made between allele and genotype frequencies in the patients and control populations. The allele frequencies were calculated from the observed numbers of genotypes. The significance of differences in the allele frequencies among groups was determined by Fisher's exact test. We used χ^2 analysis to test for deviation of genotype distribution from Hardy–Weinberg equilibrium and for comparison of differences in genotype combinations among groups. Values of $p < 0.05$ were considered to be significant. Variations in the quantitative phenotypes, such as pulmonary function and total IgE levels corresponding to the particular genotypes, were tested by Kruskal–Wallis analysis of variance and/or Fisher's exact test. Where appropriate, the 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} .

To examine the LD between all SNPs, pairwise LD coefficients D' and r^2 were calculated (Table 2) using the SNPAnalyzer 2 program (available at http://snp.istech.info/istech/board/login_form.jsp). Haplotype analysis was performed using the program PHASE v. 2.1, developed by Stephens et al. [40,41] (available free for nonprofit use at <http://www.stat.washington.edu/stephens/>). The approach underlying PHASE is a Bayesian haplotype reconstruction method using coalescent-based models, to improve the accuracy of haplotypes for unrelated individuals, although extensions to related individuals are possible. The algorithm uses a flexible model for the decay of linkage disequilibrium with distance, and it incorporates an assumption about recombination rate variation. PHASE uses Gibbs sampling, a Markov-chain Monte Carlo algorithm for the estimation of the posterior distribution. Hence, the individual haplotypes can be estimated from this posterior distribution by choosing the most likely haplotype reconstruction for each individual. Practically, PHASE was run with a single file, including genotypes of all subjects; for the c-option (two groups), 10,000 permutations were performed. Global differences in haplotype frequency profiles between both groups were determined by the permutation test, and $p < 0.05$ was considered statistically significant.

Contingency table analysis, odds ratios (OR), 95% confidence intervals (95% CIs), and significance values were estimated using Statistica version 8.0 (Statsoft Inc., Tulsa, OK) program package.

3. Results

A total of 958 subjects were included in this study. Characteristics of the study population are given in Table 1. The mean age of the control subjects was significantly higher than that of the case subjects. Total IgE levels were significantly higher in patients with allergic disorders ($p < 0.01$).

The allele and genotype frequencies of the allergic patients and controls are shown in Table 3. All four SNPs were in Hardy–Weinberg

Table 1
Clinical characteristics of the study subjects

Characteristic ^a	Allergic patients (n = 633)	Controls (n = 325)
Age (y) (mean ± SD)	32.6 ± 13.0	37.25 ± 16.0 ^a
Gender (male/female)	312/321	167/158
Smoking, no/yes (%)	83.1/16.9	70.9/29.1 ^a
Serum IgE (IU/ml) (mean ± SD)	240.7 ± 357.5	83.4 ± 47.7 ^a
Only asthma (%)	50 (7.9)	0
Only rhinitis (%)	237 (37.4)	0
Only AEDS (%)	17 (2.7)	0
Asthma and rhinitis (%)	156 (24.6)	0
Asthma and AEDS (%)	22 (3.5)	0
Rhinitis and AEDS (%)	52 (8.2)	0
Rhinitis, asthma and AEDS (%)	99 (15.6)	0
Food allergy (no/yes) (%)	82.8/17.2	100.0/0 ^a
FVC %, predicted (±SD)	95.5 ± 13.9	ND
FEV ₁ %, predicted (±SD)	85.0 ± 14.0	ND
FEV ₁ /FVC %, predicted (±SD)	81.9 ± 28.4	ND

Data are expressed as means ± SD unless stated otherwise. ND, not determined.

^a*p* < 0.01 (control vs allergic group).

equilibrium in the control and allergic groups (*p* > 0.05). No significant differences were observed between the groups in terms of C and T (−1297), C and A (−607), G and C (−137), and C and G (−140) allele or genotype frequencies (*p* > 0.05 in all cases) or between different clinical manifestation of allergy (data not shown).

Associations between allergy-related phenotypes and SNPs in the *IL-18* gene were investigated in the case group only. We looked for a possible difference in the allele and genotype frequencies among severity groups of patients with asthma. We did not find a relationship neither between the genotypes nor between the alleles and different asthma severity (data not shown). No relationship between *IL-18* variants and lung functions (measured as forced vital capacity [FVC], forced expiratory volume in 1 second (FEV₁)%, and FEV₁/FVC data) was proved (data not shown). In addition, no significant relationship between SNPs in *IL-18* gene (alone or in combination) and food allergy (yes/no) or hypersensitivity to specific food/allergen was observed, although this might be due to the low numbers of persons in the individual subgroups (data not shown). We also tested for a possible association between all four investigated *IL-18* promoter polymorphisms and the total/specific serum IgE levels. There is no evidence for the existence of significant link between total IgE levels and *IL-18* variants in this study (data not shown). However, we observed a significant association between the −607 A/C polymorphism and sensitization to *Alternaria alternata* that was more frequent in carriers of the A allele (48.5%) than in carriers of the C allele (32.9%, *p* = 0.0023, *p*_{corr} < 0.05; OR = 1.91, 95% CI = 1.24–2.95). In contrast, there were no significant associations between all other polymorphisms and the 15 allergens used in this study (data not shown). Considering that there was only one positive association of *IL-18* gene variants with specific sensitization and lack of association with serum total IgE levels, further studies are needed to clarify the true effect of this gene variant on intermediate phenotypes.

However, because it is known that interaction between different variants in the *IL-18* gene can be important for its function, we constructed the haplotypes with the four selected SNPs in this gene and tested their effects. Significant differences in haplotype frequencies between the allergic patients and healthy controls were observed (*p* < 0.01). In particular, one (−1297 C/−607 A/−137 C/−140 C) of the haplotypes occurred with significantly higher frequency in the patient group (0.0433 vs 0.0129; *p* < 0.0003, *p*_{corr} < 0.01; OR = 3.37, 95% CI = 1.59–7.14) counted as an additive effect of the four genotypes (Table 4).

4. Discussion

Asthma, allergic rhinitis, and atopic eczema/dermatitis syndrome are allergic disorders influenced by genetic predisposition and environmental factors [42]. Given the multifactorial nature of allergic diseases and the critical role of *IL-18* in the allergic response, the possible association of polymorphisms in the *IL-18* gene with allergic states has been investigated. Previously we demonstrated association of three polymorphisms within the *IL-18* gene with atopic phenotypes like elevated IgE levels and sensitization to *Alternaria alternata* in patients with allergic rhinitis [18]. In this study, we screened the same three SNPs together with a newly described putative functional polymorphism −1297 C/T alone and in combination (i.e., haplotypes) in Czech patients not only with allergic rhinitis but also with other frequent and important manifestations of allergic disorders, such as asthma and eczema.

In agreement with our first association study, we did not find any association of the four SNPs alone with asthma, rhinitis, AEDS, or their combinations. The frequencies of all four polymorphisms noted in our subjects were similar to the frequencies observed in earlier studies of white Europeans of Caucasians/white ethnicity [15,32]. Indeed, some race/ethnicity-based differences exist in the relative frequencies of the *IL-18* genotypes in European American and non-Caucasian/white subjects (estimates obtained from the Innate Immunity Programs for Genomic Applications (IIPGA) database, available at <http://www.innateimmunity.net> and Hapmap (available at <http://www.hapmap.org>)). However, we demonstrated differences in haplotype frequencies, especially, that the haplotype C-A-C-C (−1297/−607 A/−137 C/−140 C) was associated with allergic diseases independently of their clinical manifestations. Only one previous study has reported a significant association of *IL-18* haplotypes with allergic conditions, in particular, atopic eczema [27]. However, the associated haplotype −5304 T/−3945 T/−380 C in Korean population was different from that in this study. In addition, controversial findings regarding single *IL-18* gene polymorphisms (their rs numbers and ID used in different studies are presented in Table 5) analyses in allergic diseases/phenotypes have appeared in the literature (summarized in Table 6). For example, in a German study, *IL-18* polymorphisms, including promoter 1−137 G/C and promoter 2−133 C/G, were found to be associated with serum IgE levels and specific sensitization to common allergens and allergic rhinitis, whereas there was no significant difference in allelic frequencies between the asthmatic patients and healthy controls [15,16]. Similarly, a study in a Korean population reported that several polymorphisms of the *IL-18* gene were not associated with an asthmatic phenotype but with the specific IgE to *D. farinae* and *D. pteronyssinus* [17]. In contrast, *IL-18* SNPs were involved in susceptibility to atopic dermatitis and hay-fever in a German study [23,24]. A recent Japanese study showed a significant association of *IL-18* rs5744247C/G variant with the severity of adult asthma [43]. However, a number of other studies did not establish significant relationships of *IL-18* variants with allergic diseases [16,19,31].

Table 2
Linkage disequilibria of *IL-18* SNPs in control and allergic groups

<i>r</i> ² /D'	rs360719	rs1946518	rs187238	rs360721
rs360719 Control		0.929	0.992	0.933
Allergic		0.957	0.996	0.745
rs1946518 Control	0.548		0.899	0.725
Allergic	0.558		0.984	0.629
rs187238 Control	0.963	0.525		0.902
Allergic	0.972	0.578		0.758
rs360721 Control	0.752	0.387	0.718	
Allergic	0.504	0.266	0.512	

To examine the LD between all SNPs, pairwise LD coefficients D' and *r*² were calculated using the SNPAnalyzer 2 program.

Table 3

Genotype and allele frequencies of the IL-18 gene polymorphisms in allergic patients and controls

	<i>n</i>	Genotypes of IL-18, –1297 C/T			Allele		<i>p</i>
		C/C (%)	C/T (%)	T/T (%)	C	T	
Controls	325	26 (8.0)	131 (40.3)	168 (51.7)	0.282	0.718	NS
Allergic patients	633	42 (6.6)	247 (39.0)	344 (54.3)	0.265	0.735	
	<i>n</i>	Genotypes of IL-18, –607 A/C			Alleles		<i>p</i>
		A/A (%)	A/C (%)	C/C (%)	A	C	
Controls	325	40 (12.3)	168 (51.7)	117 (36.0)	0.382	0.618	NS
Allergic patients	633	81 (12.8)	308 (48.7)	244 (38.5)	0.371	0.629	
	<i>n</i>	Genotypes of IL-18, –137 C/G			Alleles		<i>p</i>
		C/C (%)	C/G (%)	G/G (%)	C	G	
Controls	325	28 (8.6)	130 (40.0)	167 (51.4)	0.286	0.714	NS
Allergic patients	633	39 (6.2)	252 (39.8)	342 (54.0)	0.261	0.739	
	<i>n</i>	Genotypes of IL-18, –140 C/G			Alleles		<i>p</i>
		C/C (%)	C/G (%)	G/G (%)	C	G	
Controls	325	154 (47.4)	139 (42.8)	32 (9.8)	0.688	0.312	NS
Allergic patients	633	329 (52.0)	249 (39.3)	55 (8.7)	0.716	0.284	

NS, not significant. Statistical significance for comparison of genotype or allele frequencies between the two groups was determined by χ^2 test (for genotypes) or Fisher's exact test (for alleles).

In addition, several studies have reported an effect of SNPs located in the *IL-18* promoter regions on transcriptional activity or *IL-18* production [19–21]. The most important polymorphism in promoter –137 G/C is situated in a GATA3 binding site that has been proposed to be responsible for specifically inducing the T_H2 phenotype [44]. The –607 C/A variant disrupts a potential cAMP-responsive element-binding protein-binding site [37]. The –140 C/G (–133 C/G) SNP in intron 1 is situated in an NF-1 binding site that was supposed to activate the transcription of a number of immune proteins, such as transforming growth factor (TGF)- β_1 , tumor necrosis factor (TNF) receptor 2, and *IL-1 β* [45]. The –1297 C/T polymorphism leads to loss of the OCT-1 transcription factor binding site that is involved in the regulation of several genes, including cytokines [32]. However, there is a large heterogeneity between studies in size of the fragments cloned and the results obtained. It seems likely that they are related to the responding cells or to the varying cytokine environments in the course of the allergic process [19]. The most thorough investigation into the link between *IL-18* variants and *IL-18* levels was carried out in the AtheroGene cohort. Five *IL-18* SNPs were selected and using a haplotypic approach they were found to be associated with age- and gender-adjusted *IL-18* levels, with one haplotype showing 9%

lower levels in comparison with the most common haplotype. However, haplotypes explained only 1.8% of the variability of *IL-18* levels [46]. Thus gene expression of *IL-18* seems to be extremely complex, taking into account the existence of different protein forms of *IL-18*. Given the biologic role of *IL-18*, gene–gene and/or gene–environment interactions could also be important [47].

We note that, although many potential allergic genes are emerging from candidate gene and genome-wide association studies [48,49], the vast majority of even the most promising allergic candidate genes have failed to show associations in other populations. It is important to determine whether the positive findings are replicable in other ethnic or independent populations and to examine the roles of the associated variants in the development of the allergic diseases. The present data suggest a possible modification of the susceptibility to the development of allergic diseases mediated by the *IL-18* haplotypes in the Czech population. However, we are probably dealing with a factor that can be influential only in the context of interaction with other genes (considering the low frequency of the associated haplotype). Indication that the *IL-18* gene might play a general role in predisposition for allergic disease certainly deserves further attention and explanation. Detailed in-

Table 4Frequencies of IL-18 haplotypes in both groups^c

Haplotype				Controls	Allergic patients	<i>p</i> ^a	<i>p</i> _{corr}
–1297 C/T							
–607 A/C							
–137 C/G							
–140 C/G							
C	A	C	C	0.01291	0.04332	0.000299	0.00299
T	A	G	C	0.10547	0.10625	NS	NS
T	C	G	C	0.56355	0.56133	NS	NS
C	A	C	G	0.25502	0.21386	NS	NS
T	C	G	G	0.03745	0.06079	NS	NS
C	C	C	G	0.01223	0.00269	NS	NS
4 Others ^b				0.01338	0.01176	NS	NS
^c <i>p</i> < 0.01							

NS, not significant; *p*_{corr} = *p* value with Bonferroni correction used to adjust α level according to number (*n* = 10) of independent comparisons.

^aHaplotype effect was counted as additive effect of the four genotypes.

^bFour pooled remaining haplotypes with very low frequencies of occurrence.

^cOmnibus *p* value assessed by permutation testing expresses global differences in haplotype frequency profiles between both groups.

Table 5

IL-18 SNPs and their positions, rs numbers, and IDs used in different studies

Relative position from transcript start	Absolute position (chromosome 11)	rs No.	ID (common name)
–1297 C/T	111,541,359	rs360719	–1297
–667 G/T	111,540,717	rs1946519	–656
–618 A/C	111,540,668	rs1946518	–607
–148 G/C	111,540,198	rs187238	–137
+102 T/G	111,539,949	rs360718	+113
+116 C/T	111,539,935	rs360717	+127
+3761 C/T	111,536,290	rs795467	–5304
+5120 T/A	111,534,931	rs4937113	–3945
+8138 T/C	111,531,913	rs360722	–920
+8685 C/G	111,531,366	rs5744247	–380
+8925 C/G	111,531,126	rs360721	–140 (–133)
+8926 A/G	111,531,125	rs4988359	–132
+8956 A/G	111,531,095	rs12721559	–
+13,925 A/C (Ser35Ser)	111,526,126	rs549908	+179, +105
+20,351 C/T (Phe137Phe)	111,519,700	–	+486
+20,513 C/T (Asn194Asn)	111,519,538	rs5744290	+573
+20,745 C/T	111,519,306	–	–
+20,751 T/A	111,519,300	–	–
+20,752 A/G	111,519,299	rs360727	–

Table 6
Literature review: Effect of IL-18 gene polymorphisms on allergic diseases

First author, year	n	ID polymorphism	Children vs adults	Race/nation	Association of IL-18 SNPs with disease	Association of haplotypes with disease	Association of IL-18 SNPs with allergic phenotypes
Kruse 2003	105 (25 AR)	–656 T/G –607 C/A –137 G/C +113 T/G +127 C/T –133 C/G –132 A/G	Children/adults	White	NS NS OR 2.72 (1.2–6.4) OR 2.56 (1.1–6.0) OR 3.22 (1.4–7.6) OR 2.37 (1.0–5.5) NS	Not determined	Yes – 4 SNPs (–137, +113, +127, –133) with IgE and sIgE
Higa 2003	582 (497 AB)	–607 C/A –137 G/C +105 A/C	Children/adults	Japanese	– OR 1.83 (1.37–2.26)	Not determined	NS with IgE or IL-18 levels
Heinzmann 2004	499 (230 AB)	–607 C/A –137 G/C +113 T/G +127 C/T –133 C/G	Children/adults	White	All NS	NS	Not determined
Nieters 2004	640 (108AR+AEDS, 44AR+AB, 170 AR)	–607 C/A –137 G/C	Adults	White	All NS	Not determined	Yes – with IgE levels
Liang 2005	391 (254 Atopy)	–137 G/C +113 T/G +127 CT	Adults	Mixed ● Chinese from Singapore (252) ● Malays (47) ● Indians (94)	All NS	NS	NS with IgE levels
Shin 2005	575 (435 AB)	–607 C/A –137 G/C +127 C/T –133 C/G +105 A/C +113 T/G +127 CT –137 G/C –133 C/G –132 A/G	Children/adults	Koreans + Caucasians (50) + Afr. Americans (50)	All NS	NS	Yes – with sIgE levels
Novak 2005	400 (225 AEDS)	–607 C/A –137 G/C +127 CT –137 G/C –133 C/G –132 A/G	Adults	White	OR 2.76 (0.9–8.4) OR 2.77 (0.9–8.4) OR 4.28 (1.2–14.8) OR 1.74 (0.8–3.7) NS	Not determined	NS with IgE and SCORAD score
Lee 2006	326 (160 AR)	–607 C/A	Children	Koreans	–	Not determined	Not determined
Imboden 2006	5734 (268 AB)	–137 G/C	Adults	White	OR 3.63 (1.64–8.02)	Not determined	Yes – with skin reactivity
Kim 2007	1120 (646 AEDS)	–5304 C/T –3945 T/A –380 C/G	Children	Koreans	OR 1.53 (1.19–2.10) NS NS	Yes – TTC haplotype	NS with IgE, SCORAD score with ECP levels, Eos counts
Lachheb 2007	217 (105 AB)	–607 C/A	Children	Tunisians	OR 1.55 (1.03–2.33)	Not determined	NS
Pawlik 2007	536 (231 AB)	–607 C/A –137 G/C	Not determined	White	All NS	NS	Yes – with severity of AB
Sebelova 2007	851 (539 AR)	–607 C/A –137 G/C –133 C/G	Adults	White	All NS	Not determined	Yes – with IgE levels and sIgE
Lee 2008	261 (201 AB)	+105 A/C	Children/adults	Chinese from Taiwan	OR 2.76 (1.65–4.6)	Not determined	Not determined
Kato 2009	264 (160 AEDS)	–137 G/C	Adults	Japanese	NS	Not determined	NS with IgE levels

AB, asthma bronchiale; AR, allergic rhinitis; AEDS, atopic eczema/dermatitis syndrome; OR, odds ratio; NS, nonsignificant differences; SNPs, single nucleotide polymorphism; IgE, immunoglobulin E; ECP, eosinophilic cationic protein; Eos, eosinophils.

vestigations of the connection between different haplotypes and their function in production of IL-18 would be helpful to clarify the etiology of allergic disorders.

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