ORIGINAL PAPERS

Adv Clin Exp Med 2007, **16**, 6, 735–741
ISSN 1230-025X

HANNA DANIELEWICZ[1], MAGDALENA HURKACZ[2], ANDRZEJ BOZNAŃSKI[1],
ANNA WIELA-HOJEŃSKA[2]

Polymorphism in the Promoter and Coding Region of the IL-4 Receptor Alpha-Chain Gene in Atopic Children

Polimorfizm w regionie promotorowym i kodującym gen dla łańcucha alfa receptora IL-4 u dzieci atopowych

[1] 1st Department of Pediatrics, Clinic of Pediatrics, Allergy, and Cardiology, Silesian Piasts University of Medicine in Wrocław, Poland
[2] Department and Unit of Clinical Pharmacology, Silesian Piasts University of Medicine in Wrocław, Poland

Abstract

Background. The IL-4 receptor alpha-chain locus is a candidate gene for atopy and allergic disease. Several polymorphisms have been investigated within the gene; however, the results are ambiguous. Polymorphism in the promoter region of the gene was suggested to be crucial for asthma and atopy susceptibility.
Objectives. The aim of this study was to evaluate the association of the C-3223T polymorphism in the promoter region and the I50V polymorphism in the coding region of the IL-4Rα gene with susceptibility to atopy and atopic diseases.
Material and Methods. Children diagnosed with atopic disease and having a positive IgE-dependent response (SPT, specific IgE, total IgE) and children with no features of atopy serving as a control group were recruited. The patients and controls were genotyped for both polymorphisms, C-3223T and I50V.
Results. The presence of the C-3223T mutant allele corresponded with atopy status, whereas such a relationship was not found for I50V.
Conclusions. These results imply that C-3223T may play an important role in the pathogenesis of atopy and atopic diseases (**Adv Clin Exp Med 2007, 16, 6, 735–741**).

Key words: atopy, genetic polymorphism, IL-4 receptor.

Streszczenie

Wprowadzenie. Gen dla łańcucha α receptora IL-4 jest idealnym kandydatem na gen podatności na atopię i atopowe choroby alergiczne. Polimorfizm regionu promotorowego genu jest sugerowany jako kluczowy czynnik determinujący podatność na astmę i atopię.
Cel pracy. Ocena asocjacji polimorfizmów C-3223T i I50V z podatnością na atopię i atopowe choroby alergiczne w grupie dzieci.
Materiał i metody. Do badania włączono dzieci atopowe z rozpoznaniem atopowej choroby alergicznej i pozytywnym miernikiem odpowiedzi IgE-zależnej (PTS, IgE specyficzne, IgE całkowite) oraz dzieci bez cech atopii, które stanowiły grupę kontrolną. Porównano dystrybucję genotypów i alleli dla obu polimorfizmów C-3223T i I50V.
Wyniki. Wykazano statystycznie istotną różnicę w rozkładzie genotypów i alleli dla C-3223T, podczas gdy zależności tego rodzaju nie udało się wykazać dla I50V.
Wnioski. Wyniki badań sugerują ważną rolę C-3223T w patogenezie atopii i chorób atopowych (**Adv Clin Exp Med 2007, 16, 6, 735–741**).

Słowa kluczowe: atopia, polimorfizm genetyczny, receptor IL-4.

The study was funded by financial resources of the Scientific Research Committee in 2003–2006 as a research project.

During the last 30 years, the incidence of atopic diseases, including asthma, has increased considerably. This is considered to be caused mainly by changes in environmental factors, although atopy is undoubtedly a genetically determined feature, as shown by several research projects based on genome scanning, positional cloning, and association analysis. Despite enormous efforts by researchers, the question of which genes determine susceptibility to atopy and atopic diseases remains open. The IL-4 receptor α-chain gene, located on chromosome 16 (16p12.1-p11.2) [1] represents an excellent candidate gene for such research. The alpha chain of the IL-4 receptor is an important element in the transmission pathway of a signal induced both by IL-4 and IL-13, two key immunological factors with regard to allergic processes. Therefore, the search for polymorphisms in the gene's functional regions has been of great interest to researchers since at least 1990, when the first polymorphism, characterized by an isoleucine shift to valine at 50 position (I50V) was described [2]. A substantial number of reports have been published to date, but the results thereof are, unfortunately, inconsistent. The majority of the studies were limited to the search for possible mutations related to atopy and atopic diseases to the gene's coding region. However, in more recent studies it was suggested to extend the search to the intron regions and the gene promoter [3]. In 2001, a new polymorphism (C-3223T) was described in the promoter region of the IL-4 receptor alpha-chain gene. A relationship between C-3223T and decreased level of the soluble receptor form of the IL-4 receptor (sIL-4R), a regulatory particle of ambivalent character, was found as well. The promoter polymorphism represents a potentially important factor in regulating gene function since it disrupts the sequence for transcription factors, such as ATF, TF11, CREB, and AP-1. Moreover, it was shown that C-3223T is in linkage disequilibrium with another SNP, I50V, in the gene's coding region, for which some studies showed an association with atopic asthma [4]. The aim of this study was to evaluate the association of the C-3223T and I50V polymorphisms with susceptibility to atopic diseases in children.

Material and Methods

Study Population

The patient group consisted of 40 children (42.5% girls and 57.5% boys) with an average age of 9.25 years (range: 3–16 years). Their detailed medical histories were recorded. The qualification criteria for the patients were the occurrence of allergic disease symptoms such as asthma, allergic rhinitis, or atopic dermatitis within at least 12 months prior to the study. Most of the children had symptoms of more than one allergic disease. The patients also fulfilled at least one of the following inclusion criteria: positive results of skin prick tests to at least one common environmental allergen (Allergopharma) and/or an increased level of specific IgE of at least 0.7 kU/l induced by common allergens and/or an increased level of total IgE (≥ 100 IU/ml). The patient group was regarded as an atopic group due to the inclusion criteria. For the control group, 36 children (47.22% girls and 52.77% boys) with an average age of 11.14 years (range: 2–17 years) were considered. The qualification criterion for the control group was an absence of allergic symptoms in the patient's and his/her family's past medical history. All the children were recruited from the Department of Pediatrics, Allergy, and Cardiology at Wroclaw Medical University. The clinical profiles of the two groups are shown in Table 1. The study was approved by the local ethics committee.

Genotyping

DNA was extracted from peripheral blood leukocytes following standard protocols (DNAmini-kit, Qiagen). The determination of the C-3223T and I50V polymorphisms of the IL-4 receptor alpha-chain gene was performed by SSP-PCR according to the protocol described by Hackstein [5].

Statistical Analysis

Genotype and alleles frequencies were compared using the chi-squared (χ^2) test or Fisher's exact test. Logistic regression models were used to analyze associations with age, sex, and genotype as co-variables. Because of the low prevalence of homozygous variant genotypes, these genotypes were grouped together with heterozygous genotypes for logistic regression. The homozygous genotype with the higher percentage was used as the reference. Linkage disequilibrium (D') between SNP loci was measured according to Lewotin [6]. A p value of 0.05 or less was regarded as significant.

Results

Genotype and Allele distribution of IL-4Rα Polymorphisms

The distribution of the genotypes for the C-3223T and I50V polymorphisms was compliant with Hardy-Weinberg equilibrium. To assess the associa-

Table 1. Clinical characteristics of the study groups

Tabela 1. Charakterystyka dzieci w badanych grupach

Variable	n (%)
Atopic children (Dzieci z atopią)	
Total (Razem)	40
Mean age – years (Średni wiek – lata)	9.25
Girls (Dziewczynki)	17 (42.5)
Boys (Chłopcy)	23 (57.5)
Sensitization (Uczulenie)	
House dust mite (Kurz)	26 (65)
Pollens (Pyłki)	29 (72.5)
Fur (Sierść zwierząt)	12 (30)
Fungi (Grzyby)	8 (20)
Food (Pokarmy)	5 (12.5)
Urban residence (Miasto)	30 (75)
Rural residence (Wieś)	10 (25)
Mean IgE: 628.03 IU/ml	
Bronchial asthma (Astma oskrzelowa)	
Total (Razem)	22
Mean age – years (Średni wiek – lata)	9.64
Girls (Dziewczynki)	10 (45.45)
Boys (Chłopcy)	12 (54.54)
Allergic rhinitis (Alergiczny nieżyt nosa)	
Total	24
Mean age – years (Średni wiek – lata)	9.96
Girls	11 (45.83)
Boys	13 (54.17)
Atopic dermatitis (Atopowe zapalenie skóry)	
Total (Razem)	8
Mean age – years (Średni wiek – lata)	9.5
Girls (Dziewczynki)	5 (62.5)
Boys (Chłopcy)	3 (37.5)
Control group (Grupa kontrolna)	
Total (Razem)	36
Mean age – years (Średni wiek – lata)	11.14
Girls (Dziewczynki)	17 (47.22)
Boys (Chłopcy)	19 (52.77)
Urban residence	28 (77.77)
Rural residence	8 (22.22)

tion with susceptibility to atopy, the frequencies of the genotypes and alleles for the two IL-4Rα polymorphisms C-3223T and I50V in atopic children and non-atopic controls were compared. Based on statistical analysis, considerable differences in the distributions of the C-3223T alleles (χ^2, $p < 0.01$) and genotypes (CT + TT vs. CC, χ^2, $p < 0.001$) were demonstrated. Logistic regression showed that subjects with a mutated allele (CT + TT) presented an almost sevenfold greater risk of atopy than subjects in whom the CC genotype was found (Tab. 2).

There were no statistically significant differences in the distributions of the genotypes and alleles between the atopic and the control groups for the I50 V polymorphism (Tab. 3). No linkage disequilibrium was found between I50V and C-3223T ($p = 0.2$).

Association Between Atopy-Related Phenotypes and the IL-4Rα Polymorphisms

In the next stage, associations between the genotypes and alleles for both the tested polymorphisms and the occurrence of a specific disease, the type of allergen sensitization, and the place of residence (urban or rural) were analyzed. The greatest association was found for C-3223T genotypes and allergic rhinitis and asthma (Fisher's test, $p < 0.01$). The highest frequency of TT homozygotes was observed in the group of asthmatic patients compared with other diagnoses (22.73%). The greatest risk related to the CT+TT vs. CC genotype was noted for allergic rhinitis. No statistically significant results were obtained for atopic dermatitis.

Considering the type of allergen sensitization, the greatest association was shown for the CT+TT genotype and allergy to pollen and house dust mites (Fisher's test, $p < 0.001$). In logistic regression, the greatest risk was obtained for the CT + + TT vs. CC genotype and allergy to animal fur (OR 19.55), for house dust mites (OR 8.75) and pollen (OR 7.11) (Tab. 4).

Considering the place of residence, a greater association of C-3223T genotype and atopy was found in urban children (Fisher's test, $p < 0.01$) than in rural inhabitants (Fisher's test, $p < 0.05$). Conversely, a higher risk for atopy was obtained in the rural group in logistic regression, but the model was not statistically significant

For I50V, no statistically significant differences were noted in the distributions of genotypes and alleles between the study groups with regard to the character of allergic disease diagnosis, allergen sensitization type, and place of residence.

Discussion

Several studies related to the chromosome 16 region (16p12.1-p11.2) have broadened the knowledge of IL-4Rα participation in atopic disease pathogenesis, but the results obtained do not present an unambiguous answer as to the genetic determination of atopy. None of the three studies based on genome scanning demonstrated an asso-

Table 2. Frequency of C-3223T genotypes and alleles in the atopic and control groups

Tabela 2. Częstość genotypów i alleli C-3223T w grupie atopowej i kontrolnej

C-3223T	Control group (Grupa kontrolna) n (%)	Atopic group (Grupa z atopią) n (%)	*OR*** 95%*CI*	p*
CC	22 (61.11)	7 (17.5)	1.0	< 0.001
CT	11 (30.56)	27 (67.5)		
TT	3 (8.33)	6 (15)		
CT+TT	14 (38.88)	33 (82.5)	6.95 (2.33–20.67)	< 0.001 ****
C	55 (76.38)	41 (51.25)	***	< 0.05
T	17 (23.61)	39 (48.75)	***	

* χ^2 test.
** logistic regression.
*** logistic regression was not applied.
**** CT + TT vs. CC.

* test χ^2.
** regresja logistyczna.
*** nie stosowano metody regresji logistycznej.
**** CT + TT *vs.* CC.

Table 3. Frequency of I50V genotypes and alleles in the atopic and control groups

Tabela 3. Częstość genotypów i alleli I50V w grupie atopowej i kontrolnej

150V	Control group (Grupa kontrolna) n (%)	Atopic group (Grupa z atopią) n (%)	*OR*** 95%*CI*	p*
II	20 (55.56)	23 (58.97)	1.0	0.76
IV + VV	16 (44.44)	16 (41.02)	0.94 (0.4–2.79)	
I	56 (77.78)	61 (78.2)	***	0.95
V	16 (22.22)	17 (21.79)	***	

* χ^2 test.
** logistic regression.
*** logistic regression was not applied.

* test χ^2.
** regresja logistyczna.
*** nie stosowano metody regresji logistycznej.

ciation with this region (Daniles et al. 1996, Colaborative Study on the Genetics of Asthma 1997, Ober et al. 1998). However, evidence confirming the significance of this region in the pathogenesis of atopic diseases was found in a project carried out in the Huterite population, where a relationship between positive skin test reactions and the presence of the D16S401 marker was demonstrated (Ober et al. 1999). The two most commonly studied SNPs remain controversial: I50V, in which the preliminary observations were not confirmed by most researchers, and Q551R. A study considering eight polymorphisms in the IL-4Rα gene was also carried out by Melen et al. [7], but for the IL-4R α-chain gene alone the authors did not confirm any association.

The present study, based on a case-control analysis, demonstrated an association between C-3223T IL-4Rα gene variations and atopy status ($p < 0.001$). Children carrying the T-3223 mutation (homozygotes and heterozygotes) revealed an almost sevenfold greater risk of occurrence of any atopic disease. In the next stage, the analysis was continued by a more precise definition of the phenotype and narrowing down the calculations to the diagnosis of a specific atopic disease or sensitization to specific allergens. Comparing the frequencies of the genotypes and alleles in the patient groups defined in this way and in the control group, similar results were obtained ($p < 0.01$). The highest risk was noted for allergic rhinitis, whereas no statistically significant differences in genotype distribution were found for atopic dermatitis. Considering sensitization to a specific allergen group, the highest risk, associated with the C-3223T genotype, was demonstrated for allergy to animal fur, then for house dust mites and pollen, but in the first case the small size of the group induces some caution. No statistically significant differences in the frequencies of the genotypes and alleles for C-3223T were observed between controls and children sensitized for food allergens and fungi.

It was also decided to include the environmental effect, defined as the place of residence, rural or urban, within the least five years, in this analysis. However, the influence of this factor was hard to interpret due to the small size of the group of children living in a rural area.

Few studies have been carried out to date regarding C-3223T polymorphism in relation to susceptibility to atopic diseases. In 2004, a Swedish study related to haplotypes consisting of 3 SNPs (C-3223T, Q551R, I50V) confirmed a relationship between TVR haplotype (T-3223, V50, R551) and atopic asthma. The patients who were

Table 4. Association between C-3223T genotypes and atopy-related phenotypes (asthma, allergic rhinitis, atopic dermatitis, sensitization to particular allergens); odds ratios (*OR*) were calculated by logistic regression

Tabela 4. Asocjacja C-3223T i fenotypów związanych z atopią (astma, alergiczny nieżyt błony śluzowej nos, atopowe zapalenie skóry, uczulenie na dany alergen), ilorazy szans (OR) zostały wyliczone z zastosowaniem regresji logistycznej

Diagnosis of allergic disease (Rozpoznanie choroby alergicznej)	*OR* (95% *CI*)#	*p**
Asthma (Astma) n = 22	6.99 (1.87–26.08)	< 0.01
Allergic rhinitis (Alergiczny nieżyt nosa) n = 24	7.58 (2.07–27.79)	< 0.01
Atopic dermatitis (Atopowe zapalenie skóry) n = 8	4.88 (0.77–30.98)	0.18
Type of allergen sensitization (Rodzaj alergenu) House dust mites (Kurz) n = 26	8.75 (2.37–32.75)	< 0.001
Pollen (Pyłki) n = 29	7.11 (2.12–23.9)	< 0.001
Fur (Sierść zwierząt) n = 12	19.55 (2.03–188.24)	< 0.01
Fungi (Grzyby) n = 8	5.25 (0.8–33.93)	0.11
Food (Pokarm) n = 5	6.07 (0.5–74.38)	0.15

logistic regression model CT + TT vs. CC, statistically significant values are bolded, $p < 0.05$.
* χ^2 test or Fisher's exact test, CT + TT vs. CC model.

regresja logistyczna model CT + TT *vs* CC, pogrubioną czcionką zaznaczono wyniki statystycznie istotne p < 0,05.
* test χ^2 lub dokładny test Fishera model CT + TT *vs* CC.

homo- and heterozygous for T, V, and R alleles also showed a milder form of asthma and a decreased level of sIL-4R. For the T-3223 allele itself, a statistically significant relationship with decreased sIL-4R serum level and a more active form of the disease was observed. Asthmatic patients revealed higher serum levels of sIL-4 than the control group [8]. In the next study considering C-3223T, 61 SNPs were analyzed within 35 genes potentially related to an immunological phenotype corresponding to allergic diseases. The evaluation included the association between selected polymorphisms and IL-5, IL-10, IL-13, and IFN-γ production, infant wheezing, occurrence of atopic eczema in the first year of life, concentration of total IgE, eosinophils, and sensitization in the first year of life. However, a significant role of C-3223T was not demonstrated [9]. In two studies related to atopic dermatitis, an association between susceptibility to this disease and the occurrence of C-3223T alleles was confirmed. Special attention should be paid to a report by Japanese authors who undertook functional research related to the IL-4Rα promoter. In their project they identified six polymorphisms by sequencing, for which five, including C-3223T, an association with atopic dermatitis was demonstrated. In the subsequent stage they analyzed haplotypes, also confirming a relationship with this disease entity. Lastly, evaluating the influence of polymorphisms on promoter transcription activity in several independent experiments, they did not find such dependence. Interesting is the result of computer analysis for the promoter, the aim of which was to define binding sites for transcription factors. The result of this study indicated the T-3223 allele as the most probable binding region for GATA-3, a factor that is responsible for the differentiation of Th2 lymphocytes [10]. In another study related to atopic dermatitis it was shown that the C-3223T polymorphism is characteristic only for eczema in atopic patients. No association was confirmed in the patients with non-atopic eczema [11].

The coupling disequilibrium between C-3223T and I50V described by Hackstein [4] and presented in numerous studies as a polymorphism revealing a correlation with susceptibility to asthma and atopy helped to decide on a further analysis considering this correlation. However, after comparing the distributions of the genotypes and alleles of the I50V polymorphism between the atopic and control groups, statistically significant associations with atopy status, diagnosis of a specific allergic disease, or a particular type of sensitization was still not found. The results were also not influenced by consideration of sex, family history of allergic diseases, and place of residence.

I50V is one of the most "popular" polymorphisms, especially with regard to functional importance. In two extensive studies, Mitsuyasu et al. [12, 13] confirmed an association between the polymorphism and atopic asthma, increased level of total IgE, and allergy to house dust mites. They also recognized the functional significance of SNP. In 1999, Tan et al. [14] made an attempt to replicate the results of the Japanese scientists in a study based on association analysis, locating a study group within the three main ethnic groups

of Singapore. Unlike their predecessors, they showed that the I50 allele occurred with a lower frequency in the atopic group than in the control group, while V50 was quite common in the first group. Similarly, Ober [3] demonstrated that I50 is transmitted with considerably less frequency to ill subjects than the mutated V50 allele. In the year 2000, Japanese authors carried out a functional study of transfectants and peripheral blood mononuclear cells loaded with the first or the second variant, evaluating CD23 expression and IgE production after stimulation with IL-4. In the I50 transfectants the level of STAT6 activation and ε-chain transcription was higher, similarly to I50 in PBMCs, where the expression level of CD23 and IgE was increased. The authors demonstrated a statistically significant difference between the allele distributions in healthy subjects and atopic asthmatics in the tested population. Such a relationship was not found for non-atopic asthma. The I50 variant also showed a relationship with total IgE level and specific IgE level induced by house dust mite allergens [15]. In 2002, Wjst et al. [16] attempted to define a relationship between selected SNPs, including I50V, and asthma and atopy. German and Swedish families, qualified by the presence of asthmatic siblings, were tested. It appeared that none of the markers demonstrated an association with the disease and IgE level.

The results of association analysis for I50V obtained in the present study demonstrate its unclear role in the promotion of allergic diseases. The considerable difference between the association levels for C-3223T and I50V implies a greater significance of C-3223T polymorphism in the susceptibility for atopic diseases. However, the present authors' preliminary research based on a family study (TDT) for this polymorphism did not confirm association at a statistically significant level. Thus the trend for C-3223T and atopy should be further investigated in future studies.

The authors conclude that the C-3223T polymorphism is a potentially important genetic factor indicating a risk for atopy and atopic diseases. The influence of C-3223T is independent of the presence of I50V. The role of the I50V polymorphism in the pathogenesis of atopic diseases remains unclear.

References

[1] Pritchard M A, Baker E, Whitmore SA, Sutherland GR, Idzerda RL, Park LS, Cosman D, Jenkins NA, Gilbert DJ, Copeland NG, Beckmann MP: The interleukin-4 receptor gene (IL4Rα) maps to 16p11.2 –16p12.1 in the human and to the distal region of mouse chromosome 7. Genomics 1991, 10, 801–806.

[2] Galizzi J-P, Zuber C, Harada N, Gorman DM, Djossou O, Kastelein R, Banchereau J, Howard M, Miyajimae A: Molecular cloning of cDNA encoding the human interleukin 4 receptor. Int Immunol 1990, 2, 669–675.

[3] Ober C, Leavitt S A, Tsalenko A, Howard TD, Hoki DM, Daniel R, Newman DL, Wu X, Parry R, Lester LA, Solway J, Blumenthal M, King Ra, Xu J, Meyers DA, Bleecker ER, Cox NJ: Variation in the interleukin-4 receptor gene confers susceptibility to asthma and atopy in ethnically diverse populations. Am J Hum Genet 2000, 66, 517–526.

[4] Hackstein H, Hecker M, Kruse S, Bohnert A, Ober C, Deichmann KA, Bein G: A novel polymorphism in the 5' promoter region of the human interleukin-4 receptor alpha-chain gene is associated with decreased soluble interleukin-4 receptor protein levels. Immunogenetics 2001, 53, 264–269.

[5] Hackstein H, Hofmann H, Bohnert A, Bein G: Definition of human interleukin 4 receptor alpha chain haplotypes and allelic association with atopy markers. Hum Immunol 1999, 60, 1119–1127.

[6] Lewotin RC: The interaction of selection and linkage. I. General consideration: heterotic models. Genetics 1964, 49, 49–67.

[7] Melen E, Umerkajeff S, Nyberg F, Zuchelli M, Lindstedt A, Gullsten H, Wickman M, Pershagen G, Kere J: Interaction between variants in the interleukin-4 receptor alpha and interleukin-9 receptor genes in childhood wheezing: evidence from a birth cohort study. Clin Exp Allergy 2006, 36, 1391–1398.

[8] Hytonen AM, Lowhagen O, Arvidsson M, Balder B, Bjork AL, Lindgren S, Hahn-Zoric M, Hanson LA, Padyukov L: Haplotypes of the interleukin-4 receptor alpha chain gene associate with susceptibility to and severity of atopic asthma. Clin Exp Allergy 2004, 34, 1570–1575.

[9] Hoffjan S, Ostrovnaja I, Nicolae D, Newman DL, Nicolae R, Gangnon R, Steiner L, Walker K, Reynolds R, Greene D, Mirel D, Gern JE, Lemanske RF, Ober C: Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. J Allergy Clin Immunol 2004, 113, 511–518.

[10] Hosomi N, Fukai, N, Oiso N, Kato A, Ishii M, Kunimoto H, Nakajima K: Polymorphisms in the Promoter of the Interleukin-4 Receptor a Chain Gene Are Associated with Atopic Dermatitis in Japan. J Invest Dermatol 2004, 122, 843–845.

[11] Novak N, Kruse S, Kraft S, Geiger E, Kluken H, Fimmers R, Deichmann, Bieber T: Dichotomic nature of atopic dermatitis reflected by combined analysis of monocyte immunophenotyping and single nucleotide polymorphisms of the interleukin-4/interleukin-13 receptor gene: the dichotomy of extrinsic and intrinsic atopic dermatitis. J Invest Dermatol 2002, 119, 870–875.

[12] Mitsuyasu H, Izuhara K, Mao XQ, Gao PS, Arinobu Y, Enomoto T, Kawai M, Sasaki S, Dake Y, Hamasaki N, Shirakawa T, Hopkin JM: Ile50val variant of IL-4R-alpha up-regulates IgE synthesis and associates with atopic asthma. Nat Genet 1998, 19, 119–120.
[13] Mitsuyasu H, Yangihara Y, Mao XQ, Gao PS, Arinobu Y, Ihara K, Takabayashi A, Hara T, Enomoto T, Sasaki S, Kawai M, Hamasaki N, Shirakawa T, Hopkin JM, Izuhara K: Cutting edge: dominant effect of ile50val variant of the human IL-4 receptor alpha chain in the IGE synthesis. J Immunol 1999, 162, 1227–1231.
[14] Tan EC, Lee BW, Chew FT, Shek L, Tay AW, Tay AH: IL-4Ralpha gene Ile50Val polymorphism. Allergy 1999, 54, 1004–1013.
[15] Izuhara K, Yanaagihara Y, Hamasaki N, Shirakawa T, Hopkin JM: Atopy and the human IL-4 receptor alpha chain. J Allergy Clin Immunol 2000, 106, 65–71.
[16] Wjst M, Kruse S, Illig T, Deichmann K: Asthma and IL-4 receptor alpha gene variants. Eur J Immunogenet 2002, 29, 263–268.

Address for correspondence:

Hanna Danielewicz
1st Department of Pediatrics, Clinic of Pediatrics, Allergy and Cardiology
Silesian Piasts University of Medicine
Hoene-Wrońskiego 13 c
51-376 Wrocław
Poland
Tel./fax: +48 71 328 12 06
E-mail: danhil@tlen.pl

Conflict of interest: None declared

Received: 31.08.2007
Revised: 29.10.2007
Accepted: 28.11.2007