Egyptian Dermatology Online Journal
Volume 2 Number 1

Arg551 Interleukin-4 receptor α Allele and Atopic Dermatitis

Enayat Attwa, M.D., and
Amira R El Sheikh*,M.D.

Egyptian Dermatology Online Journal 2 (1): 2, June, 2006

*Departments of Dermatology &Venereology and Clinical Pathology**
Faculty of Medicine- Zagazig University. Egypt.
drenayatattwa@yahoo.com

Submitted for publication: January, 2006
Accepted for publication: April, 2006.

Abstract

Background: Atopic diseases have a strong genetic predisposition. Many attempts have been made to identify the genes related to atopy. A mutation in the human interleukin -4 receptor α (hu IL-4Rα) has been linked with atopy in human.

Objective: We examined the relationship between the variation at amino acid 551 of hu IL-4Rα and atopic dermatitis (AD).

Methods: PCR- based restriction fragment length polymorphism assay was used to investigate the relationship between the glutamine 551 Arginine (Gln551Arg) and AD. Furthermore the serum IL-4 and total IgE levels were measured by using ELISA technique.

Results: The prevalence of Arg551 in AD patients was significantly higher than in controls ($p<0.001$). Relative risk of AD among those with a mutant allele Arg551 is 7.36. Arg551 allele was significantly correlated with the disease severity ($p<0.05$) and with the serum total IgE level ($p<0.01$) but not with the serum IL-4 level ($p>0.05$).

Conclusion: The Arg551 allele of IL-4Rα is strongly associated with AD and may serve as a clinically useful marker of AD severity.

Introduction

Atopy is complex, multifactorial disorders characterized by the formation of IgE antibody in persons with a genetic predisposition. A number of atopy susceptibility genes have been identified. The difficulties of conducting genetic studies of atopy are due to in part the multiple genetic markers for atopy [1].

Interleukin-4 is a peptide secreted by T_H2 cells and mast cells; it is the major cytokine responsible for the induction of IgE synthesis by B cells. Furthermore, IL-4 acts on T_H0 cells and promotes their progression to the T_H2 phenotype; ultimately leading to the secretion of more IL-4 and other T_H2-derived cytokines. It also induces the adhesion molecules on endothelial cells which important for eosinophil migration thereby perpetuating the allergic cascade [2].

The IL-4 receptor is composed of two subunits; a 140-kd α-subunit, which binds IL-4 and transduces its growth-promoting and transcription –activating functions, and a γ chain subunit which amplifies signaling of IL-4Rα. [3]**.** Signal transduction of the receptor requires phosphorylation by intracellular kinases which phosphorylate some or all of the five conserved tyrosine (Y) residues in the cytoplasmic tail of IL-4Rα. [4].

An IL-4Rα allele was identified in which guanine was substituted for adenine at nucleotide 1902, causing a change from glutamine to arginine at position551 (numbering from the start of the mature protein) (Arg 551) in the cytoplasmic domain of the IL-4Rα protein. Arg 551 has been reported to be correlated with hyper IgE syndrome and severe atopic eczema, and occurs with a frequency of 20% in the general population. Individuals who possess 1 or 2 copies of this allele have significantly increased relative risk toward the atopic phenotype compared with the wild-type variants with glutamine at position 551 (Gln 551)[5-6].

This work had been designed for identification of the allelic distribution of the Gln551Arg polymorphism in AD and its usefulness as a clinical marker of the disease. Also, study the relation of the allele with the atopic markers (serum IL-4 and serum total IgE) and with the disease severity.

Subjects and Methods:

This study included 20 patients with atopic dermatitis of both sexes with an age ranging from 8-22 years and 10 normal control subjects (age and sex matched). All patients met the diagnostic criteria for atopic dermatitis, as defined by Hanifin and Rajka [7] None of these patients had other atopic conditions (asthma, rhinitis or conjunctivitis) nor received antihistamines, or systemic or topical corticosteroids during the period of 3 weeks before clinical evaluation. The severity of atopic dermatitis was measured by using the SCORAD index [8]. AD was considered mild ,moderate, and severe forms in which the SCORAD index was less than 25, between 25 and 50 and 50 respectively.

Both patients and healthy control were subjected for the following assessment:

-**Genotyping for Arg551 and Gln551 IL-4Rα alleles** by PCR-based restriction fragment length polymorphism assay according to Rosa-Rosa et al [6] **.**

-**Serum IL4** level was measured by ELISA using the Bio-Source International, Inc. human IL-4 (hIL-4) kit according to Banchereau [9].

-**Serum total IgE** level was measured by ELISA using the Elitech IgE quantitative according to Dorrington& Bennich [10].

Genetic analysis

Genomic DNA isolated from 300 µL whole EDTA blood with the use of the PUREGENE DNA Isolation Kit purchased from Gentra (Minneapolis) was analyzed for the presence of the Arg 551 or Gln 551 alleles by PCR.

PCR was done by using the nested primers (Biosource Europe S.A., Belgium, Netherlands German) 5' - TCT CGG CCC CCA CCA GTG GCG ATC - 3' (sense) and 5' - GAG GTC TTG GAA GAG CUT ATA C - 3' (antisense) and was carried out in a total volume of 16.44µL under the following conditions : 1 cycle of 94 °C for 3 minutes, 32 cycles of 94 °C for 20 sec.,58 °C for 30 sec. and 72 °C for 30 sec., 1 cycle of 72 °C for 5 minutes and one cycle of 4 °C. Restriction digest reaction was performed in a total volume 30µl with 5 units of PvuI (Proteous Vulgaris-I) (Amersham Place Little Chalfont Buckinghamshire England HP7 9Na). The digested products were fractionated in an agarose gel matrix using the EC 360 Submarine Gel electrophoresis system (Maxicell, EC 360 M-E-C apparatus Cooperation St. Petersburg. Florida USA).The Gln551 and Arg551 alleles yielded 209bp and 186bp bands respectively.

Statistical analysis

Data were expressed as range, mean ± SD. ANOVA test, student -t-test, Fisher's exact test and correlation co-efficient (r) were used to test the significance of the results. Non parametric data was analyzed by Chi Square test. Relative risk (RR) is defined as the probability of an event of the active group divided by the probability of the event in the control group. $P<0.05$ was accepted as statistically significant.

Results

Table (1) shows the demographic data for the study groups. As regard age and sex there were no statistically significant differences between the AD and control groups ($p > 0.05$).

PCR-based Restriction Fragment Length Polymorphism assay (RFLP) of Gln551 and Arg551 alleles revealed a 209-bp band from Gln551 allele and a 186–bp band from the Arg551 allele (Figure 1).

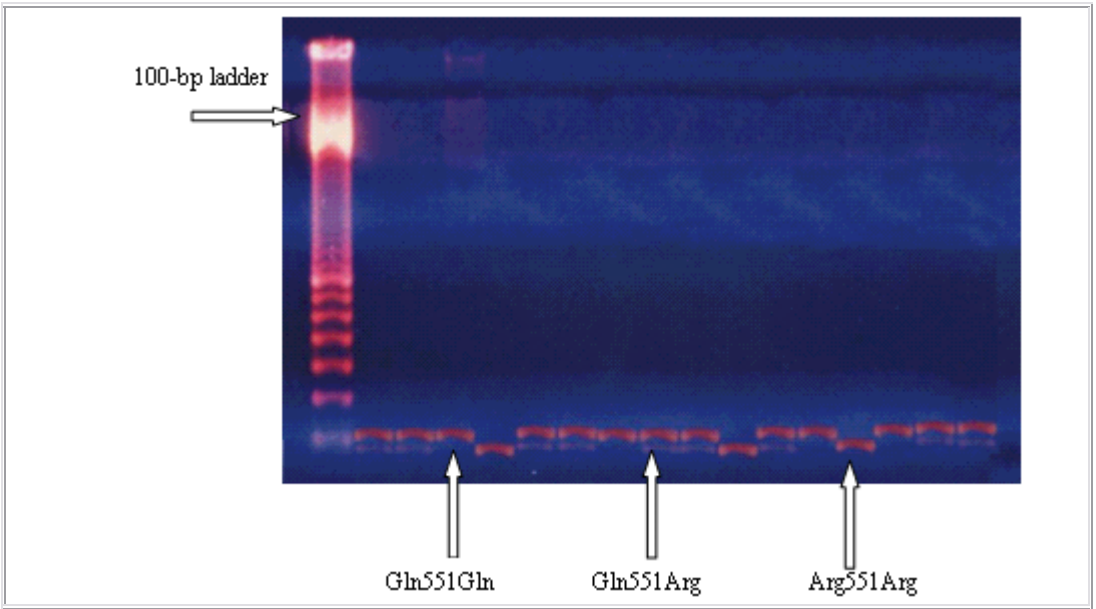

Figure 1: PCR-based RFLP assay. Arg551 and Gln551 IL-4Rα alleles correspond to 186- and 209- bp bands, respectively.

In control group, 8 persons had homozygous Gln551Gln (80%) and 2 persons (20%) had heterozygous Gln551Arg, and none had homozygous Arg551Arg . The Arg551 allele was found in only 10% (2/20) , the allele frequency for the Gln551 in 90% (18/20). Of the 20 AD patients, the homozygous Arg551Arg was found in 4 patients (20%), the heterozygous Gln551Arg in 10 patients (50%), and the homozygous Gln551Gln in 6 patients (30%). The allele frequency for Arg551 allele in AD group was 45% (18/40). There was a highly significant association of Arg551 allele in AD than in control group ($p < 0.001$). The allele frequency for the Gln551 in AD group was 55% (22/40). There was a highly significant association of Gln551 allele in control group compared with AD group ($p < 0.001$). There was also a significant association of homozygous Arg551Arg in AD group over the control group ($p < 0.05$). The relative risk for Arg551 allele in AD was 7.36. These results are shown in **Table 2**.

Of the homozygous Gln551Gln AD patients 4/6 (66.7%) had mild dermatitis, 2/6 (33.3%) had moderate dermatitis, none had severe dermatitis. There was a highly significant association of this allele with mild versus severe dermatitis ($p<0.05$, exact Fisher test). Of the homozygous Arg551Arg AD patients; severe dermatitis was found in 2/4 patients (50%), moderate dermatitis was found in 2 patients (50%), and none had mild dermatitis. These results were statistically significant for severe versus mild dermatitis ($p < 0.05$). Of the heterozygous Gln551Arg AD patients, 4/10 patients (40%) had mild dermatitis, 4/10 patients (40%) had moderate dermatitis, and 2/10 patients (20 %) had severe disease ($p > 0.05$), **Table 3**.

Table 4 shows the difference in serum IL-4 and serum total IgE levels between patients and control group. There was a highly significant increase of serum IL-4 and serum total IgE in AD group ($p < 0.001$).

The difference in serum IL-4 level in AD patients according to the severity of the disease and different alleles was not significant (p>0.05), however, in serum total IgE the difference was significant according to the severity of the disease and different alleles (p<0.001 and p<0.01 respectively**) (Table 5&6)** .There was no statistically significant correlation between serum IL-4 values and the SCORAD in AD patients (r = 0.243, p= 0.303)**(Fig.2)**. There was a highly significant positive correlation between serum total IgE and the SCORAD in AD patients (r = 0. 924, p < 0.001) **(Fig. 3).**

Table (1): Demographic data in the studied groups.

	Control (N=10)		AD patients (N=20)	
Age (yrs) Mean± SD	15.2±5.45		13.4±4.30	
t **P**	0.987 >0.05 NS			
Sex	No.	%	No.	%
Male **Female**	7 3	70 30	12 8	60 40
X2 **P**	0.17 >0.05 NS			

Table (2): Frequency of Arg551 and Gln551 IL-4Rα alleles in atopic dermatitis versus control group.

Population	Gln551Gln	Gln551Arg	Arg551Arg
Atopic dermatitis (n=20) No. % Alleles (n=40) No. Allele frequency (%)	 6 30 Gln551 22 55	 10 50	 4* 20 Arg551 18 45**
Control group (n=10) No. % Alleles (n=20) No. Allele frequency (%)	 8 80 Gln551 18 90	 2 20	 0 0 Arg551 2 10

Relative risk for Arg551 allele and atopic dermatitis is 7.36.
*p value for Arg551Arg is 0.03 between atopic dermatitis patients and controls (Exact Fisher test).
**p value for Arg551 allele is < 0.001 between atopic dermatitis patients and controls (chi square test).

Table (3): Effect of Arg551 and Gln551 IL-4Rα allelic variant on atopic dermatitis severity.

Dermatitis severity	Gln551Gln	Gln551Arg	Arg551Arg
Mild	4 (66.7%)	4 (40%)	0 (0%)
Moderate	2 (33.3%)	4 (40%)	2 (50%)
Severe	0 (0%)	2 (20%)	2 (50%)
***p* value:** severe vs mild	0.02	0.69	0.03

Mild: SCORAD ≤ 25.
Moderate: SCORAD 25-50.
Severe: SCORAD >50

Table (4): Serum IL-4 levels (pg/mL) and total IgE levels (IU/mL) in the studied groups

	Control (N=10)	AD patients (N=20)
IL4		
range	(13.9-38.23)	(55.28-81.97)
Mean± SD	27.06±7.27	68.69±7.44
t	14.558***	
P	<0.001 HS	
IgE		
range	59.75-149.1	192.3-479.2
Mean± SD	102.12±30.59	296.45±80.9
t	7.286***	
P	<0.001 HS	

Table (5): Serum IL-4 (pg/mL), and total IgE (IU/mL) in AD patients according to the severity of the disease

	Mild (no.=8)	Moderate (no.=8)	Sever (no.=4)	F	P
IL-4	67±7.7	69.23±8.24	77.7±14.13	0.801	> 0.05 NS
IgE	225.27±19.54	306.6±42.51	418.47±51.99	36.596***	<0.001HS

F: ANOVA test which compares the means of several groups.

Table(6): Serum IL-4 (pg/mL), Serum total IgE (IU/mL) and different alleles in atopic dermatitis group (n= 20).

	Gln551Gln (N=6)	**Gln551Arg (N=10)**	**Arg551Arg (N=4)**	**F**	**P**
IL-4	66.4±8.6	70.6±8	67.2±2.48	0.675	> 0.05 NS
IgE	243.36±48.77	278.05±66.92	396.57±70.25	7.597**	<0.01S

F: ANOVA test which compares the means of several groups.

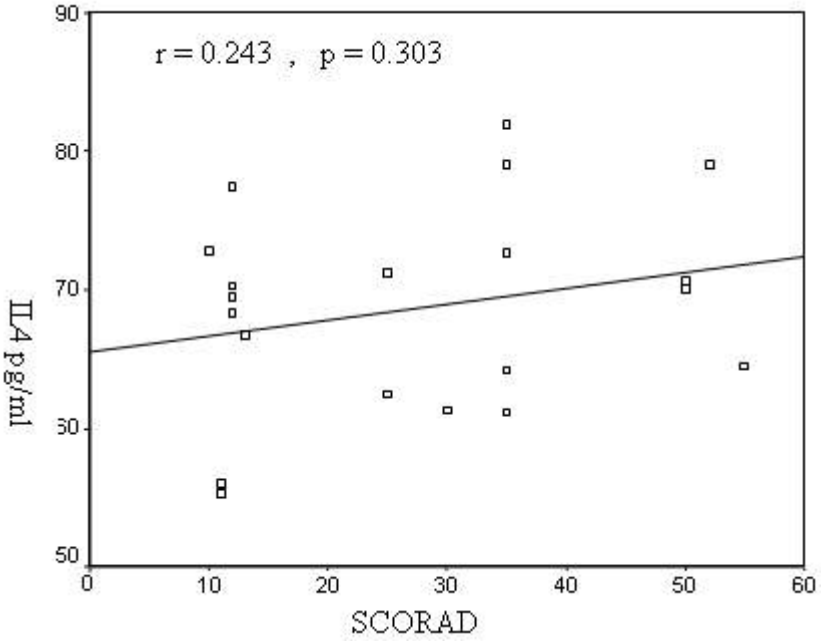

Figure 2: Correlation between serum IL-4 and SCORAD in AD patients

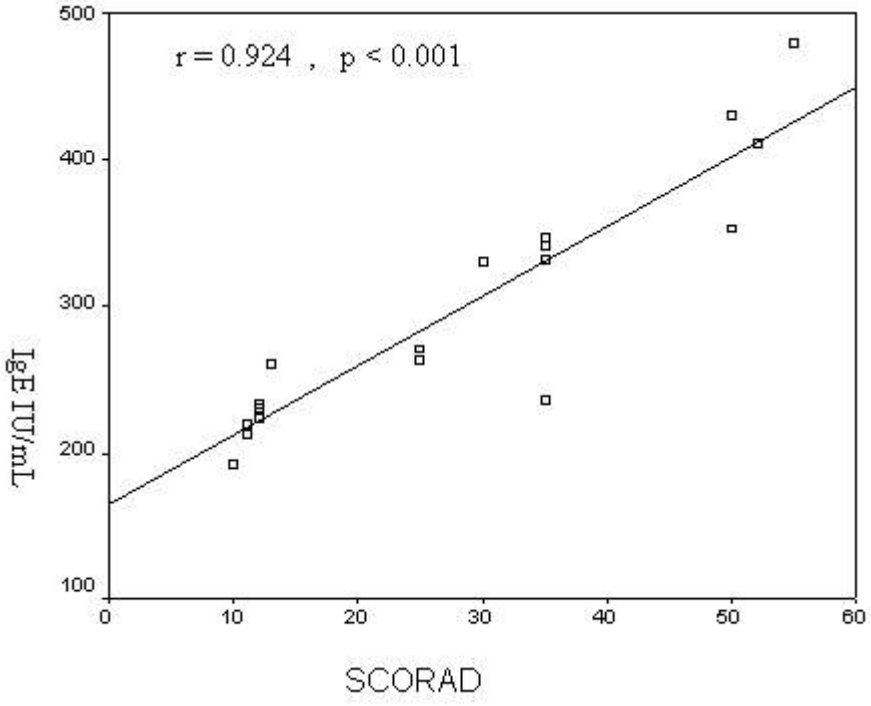

Figure 3: Correlation between serum total IgE and SCORAD in AD patients.

Discussion

It is increasingly evident that many different genes influence the development of atopy. Three different classes of disease-associated genes have been described: susceptibility genes that are strongly associated with atopy and likely play a causative role, disease-modifying genes that are not causative but modify the phenotype of the disease, and drug-modifying genes that alter the response to pharmacologic agents in affected individuals [6].

In current study, Arg551 allele acts as an atopy susceptibility gene, as the allele frequency for Arg551 allele in this study was 45% in AD group compared with 10% in the control group. Thus individual carries Arg551 allele has 7.36–fold enhanced risk toward AD than does the individual with Gln551 allele. Furthermore, there was a strong association of the homozygosity of Arg551 allele and AD, as 20% of our AD patients were homozygous while none of the control was homozygous for the Arg551 allele.

In agreement with the present study, some authors [11-13] reported that the Gln 551Arg allele frequency was more common in patients with AD than the controls, while these results conflict with others [14-17].

The suggested molecular mechanism underlying the observed enhanced signaling with Gln551Arg mutation and the association with Arg551 allele with atopy is that the substitution of arginine for glutamine at position 551(numbering from the start of the mature protein) alters the binding profile of the adjacent phosphorylated tyrosine residue (Y550) and decreases the binding of phospho-tyrosine phosphatases (SHP-1). SHP-1 dephosphorylates regulatory phospho-tyrosine residues and has been implicated in the termination of IL-4 receptor signaling leading to exaggerated IL-4 responses. Alterations in the dephosphorylation of signal transducers and activators of transcription (STAT-6) should have a potent effect on IL-4-mediated responses [5,18]. This explanation coincided with the recommendation of **Kamata et al,** [19] who reported that reduced SHP-1 protein expression results in enhanced IL-4R–mediated signal transduction and T_H2 cytokine production.

However, **Wang et al,** [20] noted that Arg551 allele does not have a direct effect on IL-4 signal transduction. It is possible that multiple docking sites for such a phosphatase exist on the huIL-4Rα so that altering a single site would not result in a dramatic change in signaling. It is possible that for an effect of the Arg551 allele change to be observed, an additional mutation in the huIL-4Rα or a mutation in, or amplification of one of its signaling molecules including Janus tyrosine kinase (JAK1,JAK3) and STAT-6 must

also occur.

Results of the present study revealed a significant association of the homozygosity of Arg551 allele and AD severity (50% of homozygous Arg551 of patients had severe dermatitis) thus, in agreement with previous studies it can be postulated that Arg551 allele acts as a disease-modifier. [5,6,21,22,23].

A majority of subjects identified as carrying a single copy of the mutant allele were found to have atopy, suggesting an intermediate dominant effect, with (increasing) homozygous suffering more severe form, and heterozygous more likely to develop more mild form of the diseases (gene dosage effect). However, the finding that some carriers of the Arg551 allele, including one who was homozygous, were not atopic indicates that the penetrance of this allele may be modified by other factors. These may include distinct genetic loci that impart susceptibility to or protection from atopy and environmental factors such as the level and duration of exposure to allergens [24].

This mode of inheritance conflicts with the French group [25], who reported that the Gln551Arg allele was significantly more common among atopic subjects and seemed to act as a recessive.

The inconsistent findings in the genetic studies of atopy may partly be explained by ethnic differences in nature and frequencies of genetic variants in disease susceptibility genes. It can be also speculated that ethnic differences in inflammatory genes (in addition to environmental factors) may also underlie the significant worldwide differences in the prevalence of AD. So, the controversial results may be due to interaction between the mutation and the environment. This suggestion is supported by **Callard et al,** [26] who have found that there is an association between the Arg551 polymorphism and flexural eczema in children at 6 months of age who have not had infection requiring treatment with antibiotics. Antibiotics supporting the "hygiene hypothesis" , which states that exposure to infection in childhood can protect against allergic disease . **Liu et al,** [27] gave significant evidence supporting the interaction between exposure to maternal smoking and variant Gln551Arg on risk of cat sensitization.

These controversial results pointed to the importance of determining the frequencies of single nucleotide polymorphisms in different populations before drawing conclusions from allele association studies, since the background allele frequencies may be disparate between different populations.

In the present study the serum level of IL-4 was significantly higher in AD patients group than control group ($P < 0.001$). no significant difference was found in its level between Arg551Arg,

the SCORAD ($r = 0.243$, $p > 0.05$). This indicates, that serum level of IL-4 is an indicator of the presence of atopy not the disease severity. Previous studies [28,29] have also reported a significant increase in serum level of IL-4 in AD patients than controls.

Grewe et al, [30] tried to explain the absence of correlation of IL-4 with the atopic disease severity; the authors stated that IFN-γ but not IL-4 has been correlated with the clinical severity of AD. This may be related to the capacity of IFN-γ to enhance eosinophil viability, augment eosinophil activation and cytotoxic activity, activate vascular endothelial molecules, which increase the infiltration of eosinophils, thereby contributing to AD. This is supported by **Ochiai et al,** [31] who found inverse correlation between IFN-γ:IL-4 ratio. So, the balance between T_H1 (IFN-γ) and T_H2 (IL-4) cytokine production is important, rather than the absolute levels of T_H2 cytokines, that decides clinical severity.

In the present study, there was a highly significant increase in serum total IgE in AD group as compared with the control group ($P<0.001$).Also, there was a highly significant increase in serum IgE levels in homozygous Arg551Arg, than heterozygous Gln551Arg, than the homozygous Gln551Gln ($p<0.01$). A positive correlation was found between increased serum total IgE levels and SCORAD($r=0.924$, $p<0.001$). These results indicate that serum total IgE may be used as indicator of AD and its severity. Significant higher levels of serum IgE have been found in other studies [32,33] .

An association between Arg551 allele and increased IgE level in AD was reported in many studies [5,6,34], which support the suggestion that Arg551 allele confers genetic susceptibility to atopy. On the other hand **Kruse et al,** [35] have found an association of Arg551 allele with lowered serum total IgE concentrations.

Some authors [32,36] have reported a significant correlation between dermatitis severity and serum total IgE levels, while **Wolf** [37] has found that 20% of the patients with severe atopic disease have normal or subnormal serum total IgE levels, and that the severity of the disease does not always correlate with serum total IgE levels. These findings do not reduce the importance of this antibody in the onset of the illness. A possibility is suggested here that even low IgE concentrations are capable of playing a key role in the pathogenesis of the disease, and being directly responsible for its clinical manifestations.

In conclusion**,** the Arg551 allele is an atopic dermatitis susceptibility gene as well as a disease-modifying gene that may be a useful genetic marker of the disease severity.

References

1- Mackay, I.R., and Rosen, F.S.: Advances in immunology; Allergy and allergic diseases. N. *Engl. J. Med. 343: 30-37,2001.*

2- Lordan, J.L.; Bucchieri, F.; Richter, A., et al.: Cooperative effects of Th2 cytokines and allergen on normal and asthmatic bronchial epithelial cells. Immunology. 169: 407-414, 2002.

3- Kawakami K., Taguchi J., Murata T., et al.: The interleukin -13 receptor alpha-2 chain: an essential component for binding and internalization but not for interleukin-13 induced signal transduction through the STAT6 pathway. Blood 97:2673-2679, 2001.

4- Nelms K., Keegan A.D., Zamorano J., et al.:IL-4 receptor: signaling mechanisms and biological functions. *Annu.Rev. Immunol.,17:701-738*,1999.

5- Hershey G.K.K., Friederich M.F., Esswein L.A. et al.: The association of atopy with a gain function mutation in the α-subunit of the interleukin-4 receptor. *N. Engl. J. Med. 337:*1720-1725,1997.

6- Rosa-Rosa, L.; Zimmermann N,; Bernstein, J.A.; et al.: The R 576 IL-4 receptor α allele correlates with asthma severity. *J. Allergy Clin. Immunol. 104:1008-1014,*1999.

7- Hanifin, J.M. and Rajka, G.: Diagnostic features of atopic eczyma. *Acta. Dermatol. Venareol. 92:44-*47,1980.

8- Severity Scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on atopic dermatitis. Dermatology , 186: 23-31,1993.

9- Banchereau, J.: Interleukin-4. Medecine/Science. 6:946-953,1990.

10- Dorrington, K.L. and Bennich, H.H.**:** Structure-Function Relationship in Human Immunoglobulin-E. *Immunol. Rev.41:3-*25,1978.

11- Dupre, D.; Audrezet, M.P. and Ferec, C.**:** Atopy and a mutation in the interleukin-4 receptor gene. *N. Engl. J. Med. 343:69-*70,2000.

12- Oiso, N.; Fukai, K. and Ishii, M.: Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br. J. Dermatol. 142:1003-1006,*2000.

13- Yandava C.N.; Pillari A.; Lilly C.M. et al.: An association of

interleukin-4 alpha receptor gene mutation and asthma and atopy. *Am. J. Hum. Gen . 63:89*,2005.

14- Mitsuyasu, H.; Yanagihara, Y.; Mao, X.Q.; et al**.:** Cutting Edge: Dominant Effect of Ile50Val Variant of the Human IL-4 Receptor {alpha}-Chain in IgE Synthesis. *Immunology. 162: 1227*-1231,1999.

15- Tan, E.C.; Lee, B.W.; Tay, A.W.; et al.**:** Interleukin-4 receptor variant Q576R: ethnic differences and association with atopy**.** *Clin. Genet. 56:333-334,* 1999.

16- Patuzzo, C.; Trabetti, E.; Malerba, G.; et al.: No linkage or association of the IL-4Rα gene Q576R mutation with atopic asthma in Italian families. *J. Med. Genet. 37:382-384,*2000.

17- Haagerup, A.; Bjerke, T.; Schiotz, P.O.; et al.: No linkage and association of atopy to chromosome 16 including the interleukin-4 receptor gene. *Allergy. 56:775-779,*2001.

18- Hanson, E.M.; Dickensheets, H.; Qu, K.; et al.: Regulation of the Dephosphorylation of STAT-6 participation of tyr-713 in the interleukin-4 receptor, the tyrosine phosphatase shp-1, and the proteasome. *J. Biol. Chem. 278:3903-3911,*2003.

19- Kamata, T.; Yamashita, M.; Kimura, M.; et al. : Src homology 2 domain–containing tyrosine phosphatase SHP-1 controls the development of allergic airway inflammation. *J. Clin. Invest. 111:109-119,2003.*

20- Wang, H.Y.; Shelburne, C.P.; Zamorano, J.; et al.: Cutting Edge: Effects of an allergy–associated mutation in the human IL-4Rα (Q576R) on human IL-4 induced signal transduction. *Immunology. 162: 4385*-4389,1999.

21- Deichmann, K.A.; Bardutzky, J.; Forster, J.; et al.: Common polymorphisms in the coding part of the IL-4-receptor gene. *Biochem. Biophys Res Comm 231:696-697,*1997.

22- Beghe, B.; Barton, S.; Rorke, S.; et al.: 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. 33:1111-1117,*2003.

23- Hytonen, A.M.; Lowhagen, O.; Arvidsson, M.; et al.: Haplotypes of the interleukin-4 receptor alpha chain gene associate with susceptibility to and severity of atopic asthma. *Clin. Exp. Allergy. 34:1570***-**1575,2004.

24- Peat, J.k.; Tovey, E. and Toelle, B.G.: House dust mite allergens:

a major risk factor for childhood asthma in Austria. *Am. J. Respir. Crit. Care Med. 153:141*-146,1996.

25- Ziani1, S.; Chavernoz1, N.; Morgant1, M.; et al.: The Interleukin-4 receptor variants I50V and Q576R in atopic children. Immunology. *162:541.* 1999.

26- Callard, R.E.; Hamvas, R.; Chatterton, C.; et al. : An interaction between the IL-4Ralpha gene and infection is associated with atopic eczema in young children. *Clin. Exp. Allergy. 32:990-993,2002.*

27- Liu, X.; Beaty, TH.; Deindl, PH.; et al.: Associations between specific serum IgE response and 6 variants within the genes IL4, IL13 and IL4RA in German children. *J. Allergy Clin. Immunol. 113:489-495,*2004.

28- Kaminishi, K.; Soma, Y.; Kawa, Y. et al.: Flow cytometric analysis of IL-4. IL-13 and IFN-gamma expression in peripheral blood mononuclear cells and detection of circulating IL-13 in patients with atopic dermatitis provide evidence for the involvement of type 2 cytokines in the disease. *J. Dermatol. Sci. 29:19-25,*2002.

29- Nomura, I.; Goleva, E.; Howell, M.D.; et al.:Cytokine milieu of atopic dermatitis, as compared to psoriasis, skin prevents induction of innate immune response genes. *Immunology. 171: 3262-3269,*2003.

30- Grewe, M.C.A.; Schopf, B.E.; Thepen, T.; et al.: A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. *Immunol. Today 19:359*-361,1998.

31- Ochiai, K.; Tanaba, E.; Ishihara, C.; et al.: Role of JAK2 signal transduction pathway in activation and survival of human peripheral eosinophils by interferon- gamma (IFN-γ). *Clin. Exp. Immunol. 18:340-343* ,1999.

32- Kawai, K.; Kamei, N. and Kishimoto, S.**:** Levels of serum IgE, serum soluble-Fc epsilon RII, and Fc epsilon RII(+) peripheral blood lymphocytes in atopic dermatitis. *Dermatology. 19:285-292,*1992.

33- Poljacki, M.; Jovanovic, M. and Matic, M.: Immunologic response in patients with atopic dermatitis. *Med. Pregl. 49:305*-307,1996.

34- Isidoro-Garcia, M.; Davila, I.; Moreno, E.; et al**:** IL4RA gene polymorphism (Q576R) is associated to higher total IgE levels in Spanish patients with family history of atopy. *Med.*

Clin. (Barc). 124:211-212,2005.

35- Kruse, S.; Japha, T.; Tedner, M.; et al.: The polymorphisms S503P and Q576R in the interleukin-4 receptor alpha gene are associated with atopy and influence the signal transduction. *Immunology. 96:365-371*, 1999.

36- Laske, N. and Niggemann, B.: Does the severity of atopic dermatitis correlate with serum IgE levels? *Pediatr. Allergy Immunol. 15:86-88*,2004.

37- Wolf, R.: The role of IgE in atopic diseases. *Med. Hypotheses. 14:353-355*,1984.