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Relationships Between IL-13 and IL-4 Genotypes and Aeroallergens with Risk of Allergic Rhinitis in Iranian-Azeri

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Background: Up to 40% of the world populations are affected by allergic rhinitis (AR). Interplay between genetics, epigenetics, and environmental factors leads to allergic disease.
Objective: In this study, we evaluated the accompaniment between polymorphic variants of *IL-13* and *IL-4* and aeroallergens among Iranian-Azeri children and adolescent in AR's risk.
Methods: Five-hundred AR patients and 300 healthy individuals were enrolled in this study after diagnosis via blood testing for IgE and skin prick test by subspecialty of Allergy and Immunology from Azerbaijan, northwest of Iran, from 2017 to 2019. Genomic DNA was prepared from all samples for genotyping of *IL-4* and *IL-13*.
Results: We identified genetic variation of *IL-13* and *IL-4* and important aeroallergens that could increase the AR risk during childhood and adolescent. The risk of AR increased in the subjects with +2044GA genotype of *IL13* [adjusted odds ratio (OR), 1.80; 95% confidence interval (CI), 0.97–3.33] and −590CT genotype of *IL4* (adjusted OR, 1.94; 95% CI, 1.00–3.87) in childhoods, compared with the control subjects. However, none of genotypes and allele frequencies of *IL4* −590C/T and *IL13* +2044G/A polymorphisms revealed significant variation between the AR patients and controls in adulthood. The frequency of sensitization to pollens was high in all genotypes of *IL4* −590C/T and *IL13* +2044G/A polymorphisms in both age groups of AR patients.
Conclusion: AR is considered to be the most common form of atopic disease. Susceptible individuals had family history of allergic disease and indicated sensitivity to various environmental factors. In this study, pollen and feather played an important role in occurrence of AR. Childhood with GA at *IL13* +2044 and CT at *IL4* −590 are at increased risk for AR. Moreover, further studies with more samples are required to confirm our findings and also to help us develop new procedure for genetically detecting more efficient proceedings of prevention and intervention.

Keywords: allergic rhinitis, risk factor, *IL-4* and *IL-13* polymorphisms, aeroallergen, childhood, and adolescent

Introduction

Allergic Rhinitis (AR) is one of the most common inflammatory disorders related to upper respiratory system, which could be initiated by an allergic immune response to aeroallergens in susceptible individuals.[1] The certain symptoms of AR are as follows: rhinorrhea (over plus nasal secretion), itching, sneezing, nasal congestion, and obstruction, which can affect the patient's quality of sleep, study, social life, and job performance.[2] AR is clinically important because it underlies many complications. Therefore, AR has been frequently comorbid with other medical conditions such as asthma, sinusitis, anosmia, otitis serositis, and nasal polyps. Lower respiratory tract infections have been rarely detected and are considered as infrequent.[3,4]

A complex interaction among genetic, epigenetics, environmental, and life-style factors contribute to the development and progression of AR.[2,5] Previous studies have also showed that single-nucleotide polymorphisms (SNPs) in those genes located on chromosome 5q region such as cytokines are linked to AR, asthma, and related feature across

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various national populations; therefore, based on such evidence, AR is a major concern in Iran, particularly in the northwest region of Iran.[6–8]

IL-4 and *IL-13* are fundamental cytokines produced by TH2 cells[9] and play an essential role in the development of allergic reaction by regulating different stages of allergic pathways. Thus, any alteration in these genes may result in different responses to diverse sensitization substances. C − 590T is a promoter polymorphism of *IL-4* that plays a key role in transcription of several cytokine genes.[10] Earlier studies indicated that *IL-4* and its receptors polymorphic variant could increase the risk of asthma interaction with environments associated with smoking and pets.[11]

IL-13 +2044G/A is a SNP in the coding region (CR) of this gene, which is located on exon 4 and causes the Arg be replaced by Gln at the position 130 of the mature protein.[12–14] Previous studies showed interaction of mold exposure with *IL13* +2044G/A polymorphism appears to increase the risk for AR during infancy.[15] Investigating these SNPs and their interactions with environmental factors may help us making new procedure for genetically detecting and more efficient proceedings of prevention and intervention. The purpose of this study was to examine the association between the *IL-13* +2044G/A and *IL-4* −590C/T polymorphisms with AR's susceptibility and also to identify the relationships between genetic and aeroallergens on the development of AR in population of Iranian-Azeri.

Materials and Methods

Samples selection

All participants were diagnosed with AR following a detailed assessment by asthma and immunologist, in terms of the international ARIA guidelines. Obligatory criteria were as follows: (1) clinical criteria of moderate to severe persistent AR over the past 3 years; (2) sensitization to aeroallergens, including pollen, Chenopodiaceous, molds, mites, and feather, with a positive skin prick test (wheal diameter >6 mm); and (3) age between 5 and 30 years old. The diagnosis of moderate to severe persistent AR was performed based on clinical criteria, including nasal rhinorrhea, itching, sneezing, and congestion.

Participants received a physical examination and were requested to answer a questionnaire about patients' age and sex. At the end, 500 AR patients distributed in two age ranges (childhood and adulthood) were recruited at Golgasht clinic in Tabriz, East Azerbaijan province, Iran, from 2017 to 2019. Satisfaction of participants were collected through direct interviewing and written confirmation, and the research protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (approver no. IR.TBZMED.REC.1397.564). For non-AR individuals, 300 volunteers were enrolled from the individuals who were referred to the medical diagnosis laboratory for check-up in Tabriz, Iran, with the same age range. They were also examined to rule out any allergic problems.

Molecular techniques

The genomic DNA was prepared from peripheral blood cell using standard techniques, and was subsequently used for amplification and genotyping of *IL-13* +2044G/A and *IL-4* −C590T.

Determination of the *IL-13* +2044G/A and *IL-4* −590C/T genotypes was performed by PCR-RFLP analysis.

The primer set to determine the rs20541 and rs2243250 was previously described. Genomic DNA was amplified using the designed primers as follows: forward 5′-CTTCCG TGAGGACTGAATGAGACGGTC-3′ and reverse 5′ -GCA AATAATGATGCTTT CGAAGTTTCAGTGGA- 3′ for rs20541; forward 5′- ACTAGGCCTCACCTGATACG-3′ and 5′- GTTGTAATGCAGTCCTCCTG-3′ for rs2243250. Digestion of the amplification product of rs20541 was done with 0.3 U *Nla*IV (BspLI) (New England Biolabs, Boston, MA), and incubation was conducted for 6 h at 37°C.

Then, they were visualized via acrylamide gel electrophoresis. The polymorphic *Nla*IV site was detected by RFLP that generates the fragments of 204 and 32 bp (G allele). The restriction enzyme for restriction fragment length polymorphism of rs2243250 was *Bsm*F1, which cleaves the C allele to create fragments of 209 and 45 bp in size.

DNA sequencing

Some of the polymerase chain reaction products of the *IL-13* and *IL-4* genes were sent to affirm the results of enzyme digestion to Topaz Gene Company (Korea) for direct sequencing. ChromasPro software was used for comparing the obtained sequences with a normal sequence from GenBank (National Center of Biotechnology Information), and they were then inspected for the existence of *IL-13* Arg130Gln polymorphism and *IL-4* C − 590T polymorphism (Figs. 1 and 2).

Statistical analysis

Statistical analysis of data was performed using the statistical package for social sciences, version 16.0 (SPSS, Chicago). An online Hardy–Weinberg equilibrium test (HWE) calculator was applied to examine the deviation

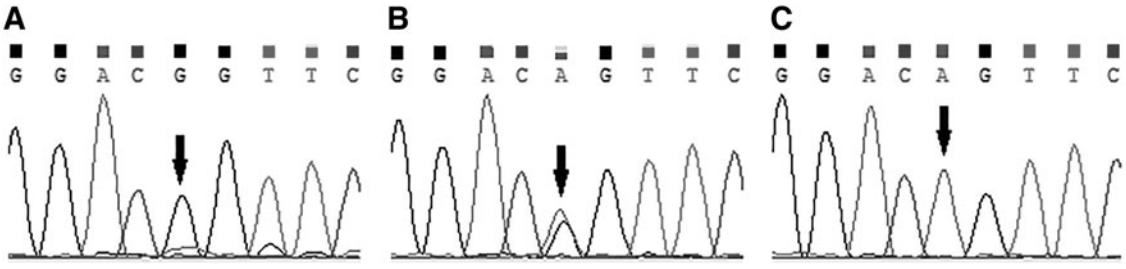

FIG. 1. DNA sequencing results for part of the fourth exon of IL-13. The *arrows* display the position of the SNP IL-13 + 2044. A: GG; B: AG and C: AA. SNP, single-nucleotide polymorphism.

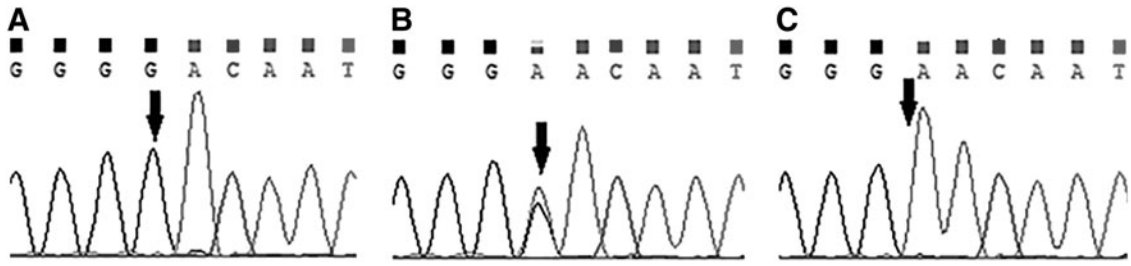

FIG. 2. DNA sequencing results for part of the promoter region of IL-4. The *arrows* display the position of the SNP IL-4 – 590C/T. A: CC; B: CT and C: TT. SNP, single-nucleotide polymorphism.

from HWE of SNPs and for comparing the *IL-4* and *IL-13* allele with genotype frequencies in patients with controls. The correlations between the genotypes or alleles of *IL-13* R130Q and *IL-4* C – 590T polymorphisms and risk of AR were estimated by calculating odds ratios (OR) with 95% confidence intervals (CI) using logistic regression. The level of <0.05 for *P*-value was considered as significant.

Results

AR clinical characteristics

In this study, some demographic features of AR patients such as age, gender, paternal history of allergic disease, history of asthma, history of allergic dermatitis, and type of AR were analyzed.

No statistical differences were observed in the value of participants' age in children and adolescent [(OR, 0.243; 95% CI, 0.345–0.611; $P=0.584$), (OR, 0.409; 95% CI, 0.409–1.494; $P=0.092$), respectively]. Also, no statistical differences were observed in the value of participants' gender in children and adolescent [(OR, 1.043; 95% CI, 0.555–1.961; $P=0.888$), (OR, 0.864; 95% CI, 0.475–1.570; $P=0.608$), respectively] between the AR patients and disease-free individuals (Table 1).

Paternal history of allergic disease and comorbidity of AR with allergic dermatitis (AD) and asthma are as follows:

In total, patients suffering from AR were 500 individuals. A history of asthma and AR were reported for 21.2% and 96.4% of the parents, respectively. Also, out of all patients, 208 (41.61%) showed allergic dermatitis. These patients were analyzed from the view point of genotypes of SNPs (Table 2).

Out of 208 patients with AR and AD, 156(75%) +2044GA/–590CT and 52(25%) +2044AA/–590CC genotypes were observed. In 75(15%) subjects, both AR and asthma were diagnosed that all of them showed +2044GA/–590CC genotypes of SNPs.

Association of *IL-13* +2044G/A and *IL4* –590C/T with AR is described below:

In this study, evaluation of relationships between rs20541 and rs2243250 genotypes in the risk AR was performed. In total, GA genotype of the *IL-13* +2044G/A ($P<0.04$) and CT genotype of *IL4* –590C/T ($P<0.03$) showed significant associations with risk for AR in children. In contrast, none of the rs2243250 and rs20541polymorphisms showed significant association with AR at both genotype and allele levels in adolescent (Table 3). In total of the investigated population, only +2044AA genotype ($P<0.01$) showed significant variation between the AR patients and healthy individuals.

Polymorphic variants of *IL-13* +2044G/A and *IL4* –590C/T and aeroallergens:

In addition, we analyzed the relationship between different genotypes of rs2243250 and rs20541polymorphisms with sensitization to different aeroallergens. In this analysis, no correlation was observed between SNPs and aeroallergens. However, in a separate state, we found pollen and feather as the most common aeroallergens in AR's patients in the northwest of Iran (Table 4).

Our study had some limitations. We have not considered sample characteristics such as body mass index and

Table 1. Age and Gender Distribution of Samples (Control and Allergic Rhinitis)

Characteristic	*Case (*n = *500)*	*Control (*n = *300)*	P	*OR (95% CI)*
Age group (years)				
5–15 (childhood)	250 (12 ± 2.41)	150 (11.87 ± 2.77)	0.584[a]	0.243 (0.345–0.611)
16–30 (adulthood)	250 (23.26 ± 4.21)	150 (23.95 ± 3.82)	0.092[b]	0.409 (0.114–1.494)
Gender				
Childhood				
Male	166 (66.4%)	101 (67.33%)		1.00
Female	84 (33.6%)	49 (32.66%)	0.888[c]	1.043 (0.555–1.961)
Adulthood				
Male	114 (45.6%)	63 (42%)	0.608[d]	1.00
Female	136 (54.4%)	87 (58%)		0.864 (0.475–1.570)

No statistical differences were observed in the value of participants' age and gender in both childhood and in adulthood.
[a,b]These data represent mean ± SD, by independent *t*-test.
[c,d]The chi-square *P*-value.
CI, confidence interval; n, number; OR, odds ratio; SD, standard deviation.

Table 2. Subjects' Characteristics

Characteristic	*Proportion (%)*
Previous history of AD	208 (41.6)
Previous history of asthma	75 (15)
Parental history of allergic diseases (asthma, AR, or AD)	475 (95)
Parental history of AR	482 (96.4)
Parental history of asthma	106 (21.2)
Type of AR	
Seasonal	153 (30.6)
Perennial	347 (69.4)

AD, allergic dermatitis; AR, allergic rhinitis.

socioeconomic level status. Cross sectional in design limited us to make conclusions on relationships between AR and risk factors. In contrast to the limitations, our study has also many strengths. First, our subjects were matched for sex and age to adjust the effects of these variables. Second, the total subjects were selected by a questionnaire survey from the entire population of the northwest of Iran, and sampling was completely performed randomly. Third, all the sample individuals were chosen using the clinical evaluation and SPT diagnosis by subspecialty of Allergy and Immunology. Therefore, AR samples and healthy controls were strictly distinguished.

Discussion

Molecular studies indicate that genetic susceptibility and environmental factors may be considered to be fundamental issues in the pathology of AR. In the previous studies, the critical role of cytokines in the development and severity of inflammatory disease has been reported. The associations between *IL-4* and *IL-13* gene polymorphisms and increased risk of atopic disease have been extensively studied.

In the current case—control study, we appraised the role of *IL-13* +2044 G/A and *IL-4* −590 C/T SNPs in AR patients in the northwest of Iran.

In the present study, by comparing the patients in case group with control group, significant differences were exhibited between −590CT genotype and AR risk in children. Similarly, it has been shown that the polymorphisms in the *IL4* gene are likely to be involved in the development of asthma, AR, and the regulation of total serum IgE.[16,17] Correspondingly, another study indicated that polymorphic variants in the *IL-4* and *IL-4*Ra chain genes might confer susceptibility and modulate severity of atopy and asthma in a Caucasian population.[18] Also, a case—control study suggested that *IL-6*, TNF-a, and *IL-4* gene polymorphisms may affect the susceptibility to idiopathic nephrotic syndrome.[19] Moreover, a pilot study indicated possible involvement of *IL-13* +2044G/A SNP and increased risk for development of AR. Furthermore, in the same study, it has been shown that *IL-4* T589C, *IL-4*RA I50V, and *IL-4*RA Q576 polymorphisms are unlikely to be associated in the development of AR.[20] Also, based on our results, there is an association between +2044GA genotypes of the variant R130Q belonging to the fourth exon of *IL-13* with AR in children. In contrast, another recent study suggested that *IL-13* R130Q polymorphism had no association with risk of AR; also, it showed no involvement with cedar pollen AR and levels of serum IgE. Furthermore, a case–control study consisting of 214 atopic patients and 120 controls suggested that G + 2044A polymorphism in *IL-13* is not considered as a risk factor for asthma and AR.[7]

Similar to our results, in a joint project performed in New York and Malaysia, the results established that the GA heterozygotes genotype carriers of A allele genotype and A allele had an increased risk for developing AR.[20] A meta-analysis involving 2,153 cases and 3,931 controls also indicated that *IL-13* SNP rs20541 was associated with AR, and suggested that *IL-13* SNP rs20541 has an effect on the

Table 3. IL-13 and IL-4 Gene Polymorphisms Among Allergic Rhinitis Patients and Controls

	Childhood (5–15)				*Adult (16–30)*			
Genotype	*Case* n *(%)*	*Control* n *(%)*	*OR (95% CI)*	P	*Case* n *(%)*	*Control* n *(%)*	*OR (95% CI)*	P
+2044 GG	119 (47.6)	88 (58.7)	1 (reference)		132 (52.8)	79 (52.7)	1 (reference)	
+2044 GA	129 (51.6)	53 (35.3)	1.803 (0.976–3.337)	0.043	105 (42)	52 (34.7)	1.208 (0.642–2.276)	0.530
+2044 AA	2 (0.8)	9 (6)	0.164 (0.004–1.711)	0.092	13 (5.2)	19 (12.7)	0.409 (0.119–1.338)	0.1
+2044 G allele frequency	367 (73.4)	229 (76.33)	1 (reference)		369 (73.8)	210 (70)	1 (reference)	
+2044 A allele frequency	133 (26.6)	71 (23.66)	1.172 (0.589–2.335)	0.628	131 (26.2)	90 (30)	0.828 (0.426–1.608)	0.550
−590 CC	137 (54.8)	98 (65.3)	1 (reference)		178 (71.2)	105 (70)	1 (reference)	
−590 CT	101 (40.4)	37 (24.7)	1.949 (1.007–3.876)	0.033	53 (21.2)	41 (27.3)	0.763 (0.376–1.547)	0.420
−590 TT	12 (4.8)	15 (10)	0.572 (0.156–1.998)	0.335	19 (7.6)	4 (2.7)	2.767 (0.594–15.05)	0.147
−590 C allele frequency	375 (75)	233 (77.66)	1 (reference)		409 (81.8)	251 (83.66)	1 (reference)	
−590 T allele frequency	125 (25)	67 (22.33)	1.158 (0.574–2.342)	0.659	91 (18.2)	49 (16.33)	1.140 (0.515–2.527)	0.727

GA genotype of the IL-13 + 2044G/A and CT genotype of IL4 − 590C/T showed significant associations with risk for AR in childhood. But none of rs2243250 and rs20541polymorphisms showed significant association with AR at both genotype and allele levels in adulthood.
AR, allergic rhinitis; CI, confidence interval; n, number; OR, odds ratio.

TABLE 4. GENETIC VARIATIONS AND AEROALLERGENS

	Childhood (%)					*Adult (%)*				
	Pollen	*Chenopodiaceous*	*Molds*	*Mites*	*Feather*	*Pollen*	*Chenopodiaceous*	*Molds*	*Mites*	*Feather*
+2044 GG	51 (42.85)	21 (17.64)	7 (5.88)	17 (14.28)	23 (19.32)	49 (37.12)	31 (23.48)	6 (4.54)	18 (13.63)	27 (20.45)
+2044 GA	55 (42.63)	23 (17.82)	6 (2.32)	19 (14.72)	26 (20.15)	36 (34.28)	23 (21.90)	4 (3.80)	14 (13.33)	31 (29.52)
+2044 AA	1 (50)	0	0	0	1 (50)	5 (38.46)	3 (23.07)	0	1 (7.69)	4 (30.76)
−590 CC	58 (42.33)	23 (16.78)	10 (7.29)	19 (13.86)	27 (19.70)	69 (38.76)	39 (21.91)	7 (3.93)	21 (11.79)	47 (26.40)
−590 CT	42 (41.58)	17 (16.83)	7 (6.93)	15 (14.85)	20 (19.80)	19 (35.84)	11 (20.75)	2 (3.77)	6 (11.32)	15 (28.30)
−590 TT	5 (41.66)	2 (16.66)	1 (8.33)	1 (8.33)	3 (25)	6 (31.57)	4 (21.05)	1 (5.26)	2 (10.52)	6 (31.57)

Pollens and feather were the most common sensitization in AR patients in all type genotypes of IL4 (rs224325) and IL13 (rs20541) polymorphisms in the northwest of Iran.
AR, allergic rhinitis.

risk of developing AR among Asians.[21] A population-based case–control study conducted in a Chinese population reported that the *IL13* and *IL4*RA polymorphisms may not have significant association with mite sensitized.[22]

A previous study suggested that GG genotype of *IL-13* 130A/G cytokine gene might be involved in increasing of the allergen-specific IgE and *IL-13* cytokine serum levels; therefore, *IL-13* may be considered to be important in the monition of asthma.[23] Furthermore, it has been shown that polymorphism *IL13* +2044G/A and mold exposure during infancy appear to have mutual participation in the development of AR. These findings also presented that early-life exposures in individuals with genetic susceptibility can affect the development of AR.[15] Protective role of SNPs in *IL-13* and *IL-10* against glioma through induction of an allergic status has been shown in the previous case–control study.[13] Meantime, a meta-analysis study indicated that R130Q polymorphism of *IL-13* gene bestow a genetic susceptibility for cancer, particularly for glioma. Accordingly, the *IL13* rs1800925 polymorphism may be associated with glioma risk.[24] In this study, we also evaluated the sensitivity to common aeroallergens in patients with AR in the northwest of Iran; therefore, the results indicated that pollens and feather were the most common sensitizations in AR patients in all type of *IL4* and *IL13* polymorphic variants in this area. Similar results were reported from allergic patients in other parts of Iran. Likewise, the hypersensitivity to pollen, dust mites, and cockroach was very common in Shiraz, Fars province, Southwest of Iran.[25]

In conclusion, this study provides an insight that probably GA +2044 and CT −590 SNPs were associated with AR in children; however, it has also showed that rs20541 in the CR of *IL-13* and rs2243250 in promoter region of *IL-4* was not associated with the risk of AR in adolescent in the northwest of Iran. This study can also be beneficial in finding the best specific allergens for immunotherapy in this area. More well-provided studies with numerous samples in relationship to AR status on different ethnicities are required to confirm these findings and are also needed to evaluate more variations in SNPs in different cytokine genes for careful inference.

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Ethics Approval and Consent to Participate

The research protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, Iran (IR.TBZMED.REC.1397.564).

Author Disclosure Statement

No competing financial interests exist.

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