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Association of Rantes Gene -403 G/A Polymorphism with Allergic Rhinitis Patients

[1]Nahla A. Melake and [2]Magdy A. Salama

[1]Department of Medical Microbiology And Immunology,
Faculty of Medicine, Menoufia University, Egypt
[2]Department of Neck Surgery and Head, Otorhinolaryngology,
Faculty of Medicine, Menoufia University, Egypt

Abstract: Currently allergic rhinitis is accepted to be multi factorial disease. Inherited susceptibility plays a major role along with the other environmental factors in the development of this disease. Therefore, it is important to search for genetic markers, associated with the development of allergic rhinitis that enables us to understand the pathogenesis, treatment and prevention of the disease. This work pursues molecular analysis of polymorphous variants of RANTES -403 G/A gene and evaluates its genetic marker in the development of allergic rhinitis. This was done by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The results revealed increases the frequency of A-403 allele among allergic rhinitis patients with significantly difference as compared to the control subjects ($P < 0.001$). The frequency of homozygotes (A/A) allele was significantly higher among allergic rhinitis patients with nasal polyps and asthma than other comorbid disorders ($P < 0.001$). This suggests the association between the gene under study and the development of allergic rhinitis. RANTES A-403 may increase genetic susceptibility to allergic rhinitis and may be used as predictor gene set for allergic rhinitis and in genomic analysis. However, further population and functional studies are necessary to clarify the roles of the polymorphisms in allergic rhinitis.

Key words: RANTES Gene -403 G/A % Allergic Rhinitis % Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) % Single Nucleotide Polymorphisms (SNPs)

INTRODUCTION

Allergic rhinitis is an inflammation or irritation of the mucous membrane lining of the nose that is caused by an allergic reaction. It is typically characterized by nasal congestion, rhinorrhea and sneezing [1].

In allergic rhinitis, numerous inflammatory cells, including mast cells, CD4 positive T cells, B cells, macrophages and eosinophils, infiltrate the nasal lining upon exposure to an inciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, moulds and pollens). The T cells infiltrating the nasal mucosa are predominantly T helper (Th2) in nature and release cytokines (e.g. IL-3, IL-4, IL-5 and IL-13) that promote immunoglobulin E (IgE) production by plasma cells. IgE production, in turn, triggers the release of mediators, such as histamine and leukotrienes, which are responsible for arteriolar dilation, increased vascular permeability, itching, rhinorrhea (runny nose), mucous secretion and smooth muscle contraction [2, 3].

Allergic rhinitis is often associated to other atopic diseases that possess a genetic basis, such as allergic asthma or atopic dermatitis. However, it must be stressed that genetic studies are complicated in allergic rhinitis, for a number of reasons. On one hand, the disease derives from the global effect of a series of genes considered individually. On the other hand, there are interactions among these genes that influence the final outcome. Lastly, there are interactions among the possible causal genes and a range of environmental factors that have not yet been clearly established. To this purpose it could be added possible epigenetic effects, defined as those inheritable changes in gene expression, occurring without actual modification in the genic DNA sequence [4].

Corresponding Author: Nahla A. Melake, Department of Immunology and Medical Microbiology, Faculty of Medicine, Menoufia University, Egypt.

Single nucleotide polymorphisms (SNPs) are the most common form of DNA sequence variation. SNPs are highly abundant, stable and distributed throughout the genome. SNPs are an increasingly important tool for the study of the structure and history of human genome and they are also useful polymorphic markers to investigate genetic susceptibility to disease or to pharmacological sensitivity [5].

RANTES is a member of a large family of cytokines, called chemokines, which are thought to play a regulatory role in inflammatory processes. It is a potent chemo-attractant for monocytes, lymphocytes, eosinophils and basophils [6]. RANTES is located on chromosome 17q11.2-q12 [7] that has been shown to be in linkage with asthma in several studies [8]. One common single nucleotide polymorphisms (SNPs) consisting of G to A exchange at position -403 in the promoter of RANTES gene, has been associated with asthma [9], atopy and elevated levels of total IgE. A significant higher constitutive transcriptional activity of the A-403 expressing promoter was detected also in atopic dermatitis children [10].

The present study was designed to investigate the genetic influence of A-403 allele of the RANTES promoter region on the development of allergic rhinitis.

MATERIALS AND METHODS

Patients: Permission of the patients and approval from the local ethic committee were obtained for the use of the specimens. The patients' specimens were taken from ear, nose and throat (ENT) department in Menoufia Universiry Hospital, Egypt. The study group consisted of 43 patients. They had allergic rhinitis manifestations. Patients with acute rhinosinusitis, systemic diseases, those who received systemic or topical anti-allergic and anti-inflammatory treatment during the previous three months and those who underwent any operation were excluded. Also, pregnant and who had morbid obesity were excluded. The clinical diagnosis of allergic rhinitis was depended on history of paroxysms of sneezing, rhinorrhea, nasal congestion and nasal obstruction, often accompanied by itching of the eyes, nose and palate. Postnasal drip, cough, irritability and fatigue were other common symptoms at ENT examination [11]. The diagnosis was supported with skin prick test. The control group consisted of 35 healthy and age-sex matching volunteers.

Table 1: Criteria of interpretation of skin prick test [14].

+	No wheal, 3 mm flare
++	2-3 mm wheal with flare
+++	3-5 mm wheal with flare
++++	>5 mm wheal, may have pseudopodia

Skin Prick Tests: Skin prick test (SPT) was done to confirm the diagnosis and to detect the causative allergen(s) [12]. The used allergens were mixed pollens, mixed moulds, mites, pigeon, wool, tobacco, house dust, feather, eggs, fish, wheat and milk. The SPT depends on the introduction of allergen extract into the dermis resulting in an IgE mediated response, which is characterized by wheal and flare reaction after about 15-20 minutes [13]. A positive control with a histamine solution (10 mg/ml) and a salt-water negative control were applied to the forearm. The allergen on the skin was lightly pricked with the tip of a lancet to pick up the superficial layer of the skin (prick test). Grading may be expressed as a percentage of the positive histamine control or may be measured as in Table 1.

Blood Samples: By using sterile syringe, 5 ml of blood was collected for each studied subject by venipunctures in an EDTA treated tube and stored at-20°C until further analysis.

DNA Extraction and PCR Amplification: Genomic DNA extraction from whole blood samples was performed using the illustra blood genomicPrep Mini Spin Kit (Amersham Place, Little Chalfont, Buckinghamshire, UK). Genotyping of RANTES gene (-403 G/A) variants was achieved by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Amplification was done by using forward primer 5'- GCC TCA ATT TAC AGT GTG-3' and reverse primer 5'-TGC TTA TTC ATT ACA GAT GTT-3'. PCR conditions were: one cycle at 95°C for 2 min followed by 35 cycles at 95°C for 40 sec, 50°C for 40 sec and 72°C for 40 sec. A final elongation step was at 72°C for 5 min, using Mycycler TM Thermal cycler (BioRad, USA). The PCR products were then digested overnight by the MaeIII restriction enzyme (Roche) at 55 °C, separated by electrophoresis in 2 % agarose gels and detected by staining with ethidium bromide (Amresco). A DNA ladder (15.0-1000.0 bp) was used to estimate allele sizes in base pairs (bp) for the gel. In the presence of the wild-type allele, the MaeIII enzyme cuts the PCR product, resulting in two bands of 112 and 23 bp; in the presence of the mutant allele, the enzyme does not cut the PCR product (135 bp).

Statistical Analysis: Computer SPSS program version 17 was used. Data were expressed as ranges, means ± S.D. and P values. Differences were considered significant at $P < 0.05$.

RESULTS

The study group consisted of 43 patients who were between ages 18 and 62 years (median 30.16±13.9). Twenty three (53.5%) were male and 20 (46.5%) were female. The control group consisted of 35 volunteers who were between ages 23 and 65 years (median 33.5±14.2) (62.9% male and 37.1% female). The mean ages and sex rates of both groups were not significantly different ($P > 0.05$).

Table 2 summarizes the demographic features of studied patients and control cases which included; age, gender, residence (place of stay), socioeconomic status, smoking behavior, cold air stimulation, history of aspirin, penicilin or skin allergy and family history of allergic rhinitis. No relationship was found between age, gender, residence, socioeconomic status and history of aspirin, penicilin or skin allergy and allergic rhinitis complaint. History of smoking was more significantly ($P < 0.01$) found among the studied allergic rhinitis patients than controls. Both family history of allergic rhinitis and cold air stimulation were present among 46.5% and 35%, respectively with a significant difference ($P < 0.01$) compared to control subjects.

Table 3 demonstrates the comorbid disorders among allergic rhinitis patients and control subjects. The most common comorbid disorder of allergic rhinitis that was found in our patients was nasal polyps (53.5%) followed by asthma (44.2%) and sinusitis (34.9%), while the least ones were otitis media (4.7%) and obstructive sleep apnea (0.0%). There was a significant difference regarding nasal polyps and asthma ($P < 0.05$) but there was no significant difference regarding sinusitis, otitis media and obstructive sleep apnea.

Table 4 demonstrates the distribution of RANTES genotype patterns in allergic rhinitis patients in comparison to that of the control subjects. At position -403, the normal genotype G/G was predominantly detected among control subjects (88.6%). On the other hand, it was detected among 48.8% of allergic rhinitis patients. Heterozygotes G/A allele was found among 21% and 11.4% of allergic rhinitis patients and studied control subjects, respectively. While homozygotes allele A/A was found among 30.2% of allergic rhinitis patients. No homozygotes allele was detected in any of the studied control subjects. There was a significant difference of RANTES gene polymorphism among allergic rhinitis patients and control subjects. The frequency of A-403 allele was significantly higher among allergic rhinitis patients as compared to the control subjects ($P < 0.001$).

Table 5 demonstrates the distribution of RANTES genotype patterns among allergic rhinitis patients in association with comorbid disorders represented in this study. The normal genotype G/G was detected among 56.6%, 42%, 80% and 100% of allergic rhinitis patients accompanied with nasal polyps, asthma, sinusitis and otitis media, respectively. Heterozygotes G/A allele was found among 8.7%, 10.5% and 20% of allergic rhinitis patients with nasal polyps, asthma and sinusitis,

Table 2: Demographic parameters of allergic rhinitis patients and control subjects.

Variables		Allergic rhinitis (no.=43)	Control subjects (no.=35)	P value
Age		30.16±13.9	33.5±14.2	P > 0.05
Gender	Male	23 (53.5%)	22 (62.9%)	P > 0.05
	Female	20 (46.5%)	13 (37.1%)	
Residence	Rural	8 (18.6%)	10 (28.6%)	P > 0.05
	Urban	35 (81.4%)	25 (71.4%)	
Socioeconomic status:	High or moderate level	26 (60.5%)	15 (42.9%)	P > 0.05
	Low level	17 (39.5%)	20 (57.1%)	
Smoking	+ ve	15 (35%)	2 (5.7%)	P < 0.01
	- ve	28 (65%)	33 (94.3%)	
History of aspirin, penicilin or skin allergy:	+ ve	7 (16.3%)	0 (0.0%)	P > 0.05
	- ve	36 (83.7%)	35 (100%)	
Cold air stimulation:	+ ve	15 (35%)	0 (0.0%)	P < 0.01
	- ve	28 (65%)	35 (100%)	
Family history of allergic rhinitis:	+ ve	20 (46.5%)	2 (5.7%)	P < 0.01
	- ve	23 (53.5%)	33 (94.3%)	

Table 3:Comorbid disorders among allergic rhinitis patients and control subjects

		Allergic rhinitis (no. = 43)		Control subjects (no.= 35)		
Comorbid disorders		No.	%	No.	%	P value
Nasal polyps:	+ ve	23	53.5	3	8.6	P < 0.05
	- ve	20	46.5	32	91.4	
Asthma:	+ ve	19	44.2	4	11.2	P < 0.01
	-ve	24	55.8	31	88.8	
Sinusitis:	+ ve	15	34.9	5	14.3	P > 0.05
	-ve	28	65.1	30	85.7	
Otitis media:	+ ve	2	4.7	0	0	P > 0.05
	-ve	41	95.3	35	100	
Obstructive sleep apnea:	+ ve	0	0	0	0	-
	-ve	43	100	35	100	

Table 4: Distribution of RANTES genotypes GG, GA and AA among allergic rhinitis patients and control subjects

	Allergic rhinitis (no. = 43)		Control subjects (no. = 35)	
RANTES gene genotypes	No.	%	No.	%
Normal (G/G)	21	48.8	31	88.6
Heterozygotes (G/A)	9	21	4	11.4
Homozygotes (A/A)	13	30.2	0	0
Total	43	100	35	100
X2	19.6			
P value	P < 0.001			

Table 5: Distribution of RANTES genotypes GG, GA and AA among allergic rhinitis patients with comorbid disorders

	Allergic rhinitis with Nasal polyps (no. = 23)	Allergic rhinitis with asthma (no. = 19)	Allergic rhinitis with Sinusitis (no. = 15)	Allergic rhinitis with otitis media (no. = 2)	P value
Normal (G/G)	13 (56.6%)	7 (42%)	12 (80%)	2 (100%)	P < 0.001
Heterozygotes (G/A)	2 (8.7%)	2 (10.5%)	3 (20%)	0 (0.0%)	
Homozygotes (A/A)	8 (34.7%)	10 (52.5%)	0 (0.0%)	0 (0.0%)	
Total	23 (100%)	19 (100%)	15(00%)	2 (100%)	

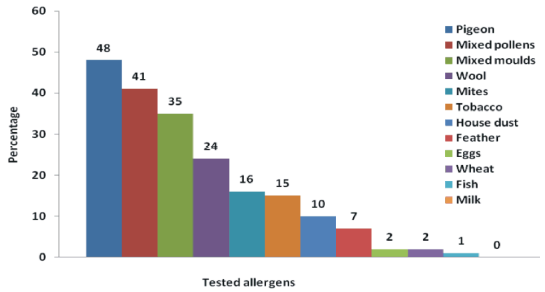

Fig. 1: Results of skin prick test to the different tested allergens among allergic rhinitis patients

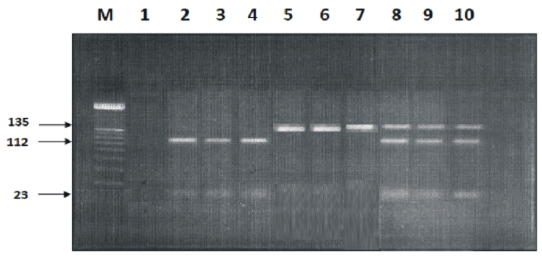

Fig. 2: Detection of SNPs of RANTES gene - 403 G/A of allergic rhinitis patients by 2% agarose gel electrophoresis. Lane (M): DNA marker (15-1000 bp); lane (1): Empty control; lanes (2 - 4): GG genotype (normal); lanes (5 - 7): AA genotype (homozygose) and lanes (8 - 10): GA genotype (heterozygose).

respectively. On the other hand, homozygotes allele A/A was found among 34.7% of allergic rhinitis patients with nasal polyps and among 52.5% with asthma. There was a

significant difference of RANTES gene polymorphism among allergic rhinitis patients with different comorbid disorders. The frequency of A-403 allele was significantly higher among allergic rhinitis patients with nasal polyps, asthma than other comorbid disorders ($P < 0.001$).

Figure 1 shows the hypersensitivity of allergic rhinitis patients to the different tested allergens by the skin prick test (SPT). The most common allergens in this investigation that patients were pigeon (48%), followed by mixed pollens (41%), mixed moulds (35%), wool (24%), mites (16%), tobacco (15%), house dust (10%) and feather (7%). The less common allergens included eggs and wheat (2% for each one), fish (1%) and milk (0.0%).

Figure 2 illustrated the bands of PCR-RFLP of SNPs of RANTES gene -403 G/A of allergic rhinitis patients by 2% agarose gel electrophoresis. The G to A transition at position -403 creates a *Mae*III restriction site. Therefore, in the presence of the wild-type allele (G/G), the *Mae*III enzyme cuts the PCR product, resulting in two bands of 112 and 23 bp and in the presence of the mutant allele, the enzyme does not cut the PCR product (135 bp) among homozygose (A/A) and revealed one band. While among heterozygose (G/A), three bands were represented at 135, 112 and 23 bp.

DISCUSSION

Chemokines play important roles in the pathogenesis of many inflammatory diseases, such as rheumatoid arthritis, asthma, multiple sclerosis, transplant rejection and atherosclerosis [15]. Chemokine genes are probably one of the most polymorphic sets of genes in the immune system and it is becoming increasingly clear that chemokine polymorphisms influence the immune response to a remarkable extent. As the genome project progressed and the abundance of SNPs became evident, databases began to record SNPs and now millions of them are registered [16].

The number of reports on disease-associated SNPs including members of the chemokine superfamily is increasing and will probably continue to rise during the next few years, as the importance of chemokines in the immune response gains recognition [16]. Allergic rhinitis-associated SNPs were reported at different genes as among CCL5 in gene -28 C/G located at promoter region (rs2280788) [17] and among CCL26 in gene +2497 T/G located at 3'UTR region (rs2302009) [18] in Korean population. Also, polymorphism was investigated among CCL5 in -403 G/A located at promoter region (rs2107538) by Kim *et al*, 2004, in Korean population [17] and in this study, the possibility of association of RANTES gene -403 G/A polymorphism with the development of allergic rhinitis in Egyptian population was investigated.

Clinical associations of RANTES G-403A with inflammatory diseases such as atopic dermatitis [19, 20] and asthma [19] have been reported.

In our study, we described an association between polymorphism within the RANTES gene promoter and risk of allergic rhinitis. The A-403 allele was found to be associated with increased risk of atopy defined as a positive skin prick test to aeroallergen (the most common allergens in our patients were pigeon followed by mixed pollens, mixed moulds and wool). Furthermore, homozygosity for this allele was found to be associated with increasing severity of allergic rhinitis by association with other comorbid disorders such as asthma and nasal polyps. In particular, subjects with the AA genotype demonstrated an increased risk of allergic rhinitis compared with those with the GG genotype. These associations were suggesting that the associations of allergic rhinitis with asthma operate through similar mechanisms. Also, this view is supported by our data showing that correlation between prick skin test positivity, RANTES homozygosity and asthma among allergic rhinitis patients. However, numbers of individuals in our study were small and therefore these data should be confirmed in larger patient scales.

In a previous study of Vasila, 2010, he found that, there was an association of polymorphous variant of RANTES - chemokine gene with the development of year-round form of allergic rhinitis in Uzbek population [21]. He revealed that, the total frequency of heterozygous or homozygous variant of mutant genotype RANTES gene carriage was equal to 34% in a conditionally healthy group and 47.7% in patients with allergic rhinitis. While in our results we found that, the total frequency of heterozygous or homozygous variant of mutant genotype of studied gene carriage was equal to 11.4% only in control subjects and was 51.2% in allergic rhinitis patients. Also, Kim and his colleagues, 2004, reported that, the frequencies RANTES A-403 allele was significantly higher in patients with allergic rhinitis than in control subjects [17].

Polymorphism in the RANTES gene was assessed for evidence of association with allergic rhinitis. From this assessment, a significant difference was observed between allergic rhinitis and controls in subjects with the RANTES AA genotype carriers. These results suggest that RANTES G-403A polymorphism is associated with the development of allergic rhinitis in Egyptian. However, further population and functional studies are necessary to clarify the roles of the polymorphisms in allergic rhinitis.

Interestingly, most polymorphisms associated with disease in the chemokine superfamily affect their inflammatory members, thus confirming that they are the genes under stronger evolutionary pressure.

CONCLUSION

It could be concluded that the study results indicated that the A-403 allele in the RANTES promoter region belong to the predictor gene set for allergic rhinitis and could be used in genomic analysis.

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