

Original Research Article

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Association between two TIM-1 Promoter SNPs (-416G>C and -1454G>A) and Allergic Rhinitis in Egyptian Patients

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ABSTRACT

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T cell/transmembrane immunoglobulin and mucin (TIM) molecules have a critical role in regulating immune responses. TIM-1 which is highly polymorphic in human has many nucleotide polymorphisms (SNPs) that have been studied for their role in allergic diseases, but the results were not consistent. The aim of study was to investigate the possible association between two TIM-1 promoter SNPs (-416G>C and -1454G>A) and allergic rhinitis (AR) in Egyptian patients sensitized to house dust mites. A further aim, was to assess the relationship between these SNPs and the level of house dust mites specific IgE. In a case-control study, a total of 30 AR patients who had positive skin prick test (SPT) to house dust mites were compared to 20-matched healthy volunteers regarding the two SNPs using restriction fragment length polymorphism (RFLP) technique. House dust mites specific IgE was measured in both groups using ELISA test and the results of both groups were compared. TIM-1 promoter SNPs (-416G>C & -1454G>A) were not significantly associated ($P > 0.05$) with AR in Egyptian patients sensitized to house dust mites. Furthermore, no significant association ($P > 0.05$) was found between the different genotypes at these SNPs and the level of house dust mites specific IgE. TIM-1 promoter polymorphisms (-416G>C & -1454G>A) do not contribute to the risk of development of AR in Egyptian patients.

Introduction

The T cell/transmembrane, immunoglobulin, and mucin (TIM) gene family was cloned in 2001 using a congenic mouse model of asthma (McIntire *et al.*, 2001; McIntire *et al.*, 2004). Since that time, evidences has accumulated which indicating that this gene family plays a critical role in regulating immune responses, including transplant tolerance, autoimmunity, the regulation of allergy and asthma, and even more the immune response to viral infections

(Rodriguez-Manzanet *et al.*, 2009; Su *et al.*, 2008). In humans, the TIM gene family has only 3 members, TIM-1, TIM-3, and TIM-4. All members of the family have a type I membrane protein characterized by identical structural motifs including a signal peptide, Ig domain, machine domain, transmembrane region, and intercellular tail with phosphorylation sites (Kuchroo *et al.*, 2003; McIntire *et al.*, 2001). The TIM gene family is located on human chromosome 5q31-33,

which has been thought to be linked to asthma susceptibility (Shek *et al.*, 2001). TIM proteins expressed in T cells has been reported to play an important role in regulating TH1- and TH2-cell-mediated immunity (McIntire *et al.*, 2001) and TIM-1 and TIM-3 polymorphisms were associated with Th1-Th2 differentiation and airway hyper reactivity (Mete F *et al.*, 2014).

TIM-1 was initially identified in 1996 as the receptor for the hepatitis A virus (HAVCR1) in monkeys (Kaplan *et al.*, 1996) and then in 1998 it was identified in humans (Feigelstock *et al.*, 1998). TIM-1 is an important susceptibility gene for asthma and allergy (McIntire *et al.*, 2003), is expressed on Th2 cells preferentially and functions as a potent costimulatory molecule for T-cell activation (Umetsu *et al.*, 2005). TIM1 is also expressed by B cells, macrophages, and dendritic cells, although its role in responses by these cell types has not been accurately established (Miranda *et al.*, 2012). The TIM-1 gene contains many sites of polymorphisms, but the one of them have been extensively studied for evaluating their role in pathogenesis of allergic diseases is exon 4 variations, though the results were not all consistent (McIntire *et al.*, 2003; Chae *et al.*, 2003; Gao *et al.*, 2005; Noguchi *et al.*, 2003; Li *et al.*, 2006). TIM-1 is highly polymorphic in human, monkey, and mouse, with single nucleotide polymorphisms (SNPs) as well as insertion/deletion variants primarily in the mucin domain in both humans and mice. Analysis of the insertion/deletion variants of TIM-1 in patients with asthma and allergy (atopic diseases) demonstrated that allelic variation of TIM-1 contributed to the risk of atopy (Yokouchi *et al.*, 2000). Many studies confirmed a role for TIM-1 in atopic diseases, but it is still unclear by what mechanism TIM-1 may play a pivotal role in the development of these diseases (Miranda

et al., 2012). The association of TIM1 with atopic diseases has been confirmed in studies of large populations in Baltimore (Gao *et al.*, 2005), Korea (Chae *et al.*, 2003), China (Wu *et al.*, 2009), and Australia (Page *et al.*, 2006). TIM4 also was associated with atopic dermatitis in a study in Australia, (Page *et al.*, 2006), and TIM3 was associated with asthma (Graves *et al.*, 2000). One study reported no association of TIM-1 with atopic asthma in Japan (Noguchi *et al.*, 2003), where HAV infection incidence is close to zero. Another study in China, where HAV infection is still common, reported an absence of association of TIM-1 with asthma, in this study patients with allergic rhinitis and atopic dermatitis were not included (Li *et al.*, 2006).

The prevalence of allergic diseases such as allergic rhinitis (AR) and asthma has remarkably increased during the past few decades world wide (Holgate. 1999). Allergic rhinitis is characterized by hyper responsiveness, overproduction of type 2 helper (TH2) cytokines, and selective eosinophil accumulation in the nasal mucosa (Kay. 2001). Allergic rhinitis is often associated to other forms of atopic diseases which have a genetic basis, such as allergic asthma or atopic dermatitis. However, genetic studies are complicated in allergic rhinitis, for many reasons. The development of allergic rhinitis shows a complex interaction between genetic predisposition and exposure to different environmental factors. 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 determine the final outcome. Lastly, there are interactions between the causal genes and a variety of environmental factors which have not yet been clearly identified. Most studies of SNPs in allergic rhinitis have been made in the last decade. Many of these

studies have been involved Asian populations, especially in Japan and Korea (Dávila *et al.*, 2009).

Many studies have previously shown up regulation of TIM-1 expression in murine models of allergic rhinitis and asthma and its association with TH2 differentiation (Mou *et al.*, 2010).

For better understanding of pathogenesis of AR, the aim of this study was to investigate a possible association between two TIM-1 promoter single nucleotide polymorphisms (SNPs), -416G>C and -1454G>A with AR Egyptian patients sensitized to house dust mites. We also investigated the relationship between the genotypes of each polymorphism and the level of house dust mites specific IgE in those patients.

Materials and Methods

This study was performed in the Microbiology and Immunology Department & Allergy and Immunology Unit, Faculty of Medicine, Zagazig University, Egypt, in the period from January 2014 to August 2014. A total of 30 allergic rhinitis patients that are sensitized to house dust mites were enrolled in this study. They were recruited from the Allergy Unit of Zagazig University Hospitals. Patients were referred to the Allergy Unit already diagnosed as allergic rhinitis patients in different ENT outpatient clinics of Zagazig University Hospitals.

All enrolled patients had positive skin prick test (SPT) for house dust mite allergenic extract. Skin prick tests were performed by the same qualified personnel using *Dermatophagoides pteronyssinus* allergenic extract (AL, Allergy Laboratories, Inc., USA) according to previously published standards (Heinzerling *et al.*, 2013). Histamine and the allergen diluent were

used as positive and negative controls, respectively. Results were evaluated within 20 min. The test was considered positive if the produced wheal had a diameter 3 mm larger than of the negative control. Examined patients were all non smokers and none of them had an upper respiratory tract infection in the 4 weeks preceding the skin test.

A total of 20 age-matched, apparently healthy volunteers were enrolled as control group. All of them had no clinical history suggestive of allergic conditions and all had negative skin test. They were chosen from the working staff in the Allergy Unit and from patients' relatives. Informed written consent was obtained from each participant before sample collection. The study was approved by the local ethical committee of Zagazig University Hospitals.

For all participants, 5 ml blood were collected and divided into two halves, where 2.5 ml were left to coagulate for serum separation while the other 2.5 ml were kept in EDTA containing vacutainer tubes to prevent coagulation. Serum samples were kept at -20°C till they were used for measuring the level of house dust mites specific IgE using RIDASCREEN Spezifisches IgE (A0249) ELISA kit (R-Biopharm AG, Germany). Genomic DNA was extracted from anticoagulated blood using QIAamp DNA minikit (Qiagen, Germany) according to the manufacturer's instructions. DNA extracts were kept at -20°C till their use. PCR reactions were performed in Biometra T gradient (Germany) thermal cycler using the following primer sets; 5'-GCA TGT TGT ACA GGA GCA TGA-3' and 5'-GCA GAC AGG CTG GTT GGT ACC-3' for -416G>C and 5'-CAG GTT GGT CTC AAA CTC CTT-3' and 5'-TTC CAA GGA GGC AGT GGT GG-3' for -1454G>A. The reactions

were performed using Maxime PCR PreMix (i-Taq) beads (iNtRON Biotechnology, Korea) in a total volume of 20µl solution containing 5µl of template DNA and 0.2 µM of each primer. An initial denaturation step at 98°C for 10 s was performed, followed by 30 cycles of denaturation at 98°C for 30 s, annealing at 65°C for 40 s in case of -416G>C or at 58°C for 40 s in case of -1454G>A, followed by extension at 72°C for 1 min, and a final extension for 10 min at 72°C. PCR products were digested using 20 units of TaqI (Invitrogen, China) for 3 h at 65°C in case of -416G>C and 20 units of MspI (Invitrogen, China) for 3 h at 37°C in case of -1454G>A. Digestion products were separated on 2% agarose gel, stained with ethidium bromide and visualized on UV transilluminator.

Statistical Analysis

This was done using Statistical Package for Social Sciences (SPSS) version 19 for data processing. Mann-Whitney U test and Kruskal-Wallis tests were used to compare non parametric data. For risk assessment, odd ratio and 95% confidence interval were applied. P value < 0.05 indicated significant results.

Results and Discussion

The general characteristics of the studied population are presented in Table 1. When house dust mite specific IgE was tested in both groups, a highly significant ($P < 0.001$) difference was found between both groups regarding the mean of specific IgE (Table 2) (6.9 ± 6.4 in patients compared to 0.76 ± 0.8 in the control group), as well as regarding the grading of specific IgE level ($P < 0.001$) (Table 3).

Two SNPs (-416 G>C and -1454 G>A) in the promoter region of TIM-1 were investigated in all participants. The

genotypes of the 2 SNPs were determined in both groups. Allele frequencies at both SNPs were compared using Chi square (X^2) test to reveal if they are associated with the susceptibility to allergic rhinitis.

Regarding the -416 G> C SNP, the CC genotype was the most frequent among both groups (Table 4) being detected in 76.6% and 85% of patients and controls, respectively. On the other hand, the CG genotype was infrequent being detected in 6.6% and 5% of patients and controls, respectively. The C allele had higher frequency in both patients (80%) and controls (87.5%), than the G allele (Table 4).

Concerning the -1454 G> A SNP, the GG genotype had higher frequency in both groups (Table 4) being detected in 63.3% and 52% of patients and controls, respectively. On the other hand, the AA genotype was infrequent being detected in 10% of each group. The G allele was more frequent than the A allele being detected in 76.6% and 77.5% of patient and control groups, respectively (Table 4). No significant difference ($P > 0.05$) in the genotype and allele frequencies of -416 G > C and -1454 G > A polymorphisms between patients and controls was demonstrated (Table 4). Furthermore, no significant association ($P > 0.05$) between certain genotypes and elevated specific IgE levels was shown (Table 5).

A remarkable research effort has focused on the genetic bases of asthma and atopic disease. As a result, studies of the genetic bases of allergic rhinitis may have been neglected to a point. More recently, however considerable attention has focused on the genes that may be implicated in AR, with particular emphasis on Asian populations. Associations have been reported between AR and certain chromosomes – the most established examples being chromosomes 2,

3, 4 and 9 where most of these studies have involved genes encoding for cytokines and their receptors, due to the reported

association of many cytokines in the pathogenesis of AR, in particular, IL-4 and its receptor.

Table.1 General Characteristics of the Studied Population

Sex	Patients No. (%)	Controls No. (%)	χ^2	P value
Male	12(40.0)	9(45.0)	0.12	0.726
Female	18(60.0)	11(55.0)		
Total	30(100.0)	20(100.0)		
Age in years	Mean±SD	Mean±SD	t test	P value
Range	25.3±9 (12-40)	26.2±12.2 (12-46)	1.21	0.276
Disease duration (months)	8.7±9.26 (2-36)			
Median				
Range				

Specific IgE	Mean ±SD	Range	MW*	Pvalue
Patients	6.9±6.4 Median=5.1	0.45-26.42	44.5	<0.001**
Controls	0.76±0.8 Median=0.31	0.05-3.07		

Table.2 Results of House Dust Mites Specific IgE in both Groups

Specific IgE	Mean ±SD	Range	MW*	Pvalue
Patients	6.9±6.4 Median=5.1	0.45-26.42	44.5	<0.001**
Controls	0.76±0.8 Median=0.31	0.05-3.07		

*MW: Mann-Whitney U test

**highly significant

Table.3 Distribution of Grades of House Dust Mites Specific IgE Level in Both Groups

Grades of IgE level	Patients No. (%)	Controls No. (%)	χ^2	P value
Negative	5(16.7)	13(65.0)	21.71	<0.001**
Low	2(6.7)	5(25.0)		
High	4(13.3)	1(5.0)		
Extremely high	19(63.3)	1(5.0)		
Total	30(100.0)	20(100.0)		

**highly significant

Table.4 Distribution of -416 G>C and -1454 G>A SNPs (Genotypes) and Allele Frequencies in both Groups

		Patients (30) No.(%)	Control (20) No.(%)	OR (95% CI)	χ^2	P value
-416 G>C SNP	CC	23 (76.6)	17 (85.0)	0.5(0.125-1.999)	0.13	0.718
	CG	2 (6.6)	1 (5.0)	0.889(0.706-1.120)	0.13	0.715
	GG	5 (16.6)	2 (10.0)	8(0.347-184.364)	0.06	0.803
Allele	G	12 (20.0)	5 (12.5)	2(0.5-7.997)	0.96	0.328
	C	48 (80.0)	35 (87.5)	1.143(0.88-1.485)		
-1454 G>A SNP	GG	19 (63.3)	13 (52.0)	1(0.08-12.557)	0.01	0.904
	GA	8 (26.6)	5 (25.0)	13.5(3.55-51.227)	0.02	0.895
	AA	3 (10.0)	2 (10.0)	0.889(0.826-0.956)	0.23	0.63
Allele	G	46 (76.6)	31(77.5)	7.309(2.548-20.97)	0.01	0.923
	A	14 (23.3)	9 (22.5)	11.213(3.723-33.768)		

OR: odd ratio; 95% CI: 95% confidence interval. χ^2 (Chi square test)

Table.5 Association between -416 G>C and -1454 G>A SNPs (Genotypes) and the Level of Specific IgE in the Studied Patients

		Specific IgE			KW*	P value
		Mean \pm SD	Median	Range		
-416 G>C SNP (Genotype)	CCn=23	7.5 \pm 7.1	4.08	0.53-26.42	0.815	0.665
	GGn=5	4.4 \pm 3.4	6.47	0.45-7.39		
	GCn=2	1.3 \pm 2	0.38	0.05-9.2		
-1454 G>A SNP (Genotype)	GG=19	7.7 \pm 7.5	4.08	0.53-26.42	0.83	0.66
	GAn=8	5.1 \pm 4.6	4.94	0.45-13.54		
	AAAn=3	6.5 \pm 2.9	6.81	3.51-9.2		

*KW= Kruskal Wallis test (non parametric test)

Most SNPs studies in AR have been carried out also in Asian populations, mostly in Japan and Korea and they involved genes encoding for molecules involved in the pathogenesis of AR as chemokines and their receptors, interleukins and their receptors, eosinophil peroxidase and leukotrienes, among others – with different results in various patient populations (Dávila *et al.*, 2009).

The critical role of T cells in the pathogenesis of allergic disease is well established. Through the production of IL-4, IL-5, and IL-13, allergen-specific TH2 cells induce IgE synthesis, eosinophil growth and

differentiation, and airway hyper responsiveness. It was proposed that the basis of allergic disease was an imbalanced TH cell response to certain allergens, characterized by predominance of TH2 cytokines over TH1 cytokines. While the role of TH2 cells in the pathogenesis of allergic disease is clear, the mechanisms underlying the predominance of these cells are less well characterized. A number of reports suggested that *TIM-1* mRNA is expressed by TH2 but not TH1 cells in humans and mice, and that *TIM-1* is up regulated by CD4+ T cells after stimulation (Mou *et al.*, 2010).

In an attempt to explain the genetic tendency of atopic diseases, numerous candidate genes residing in a syntenic chromosomal region (5q33.2) linked to susceptibility to allergy and autoimmune diseases were screened for genetic polymorphisms. *TIM-1* attracted much attention when the *TIM-1* protein was found to be the receptor for hepatitis A virus, and epidemiologic data revealed that atopic diseases were less common among children who had had hepatitis A. More recently, polymorphisms of the *TIM-1* gene were found to be linked to susceptibility to asthma in a Korean and a Caucasian-American population (Mou *et al.*, 2010).

Of the *TIM* genes, *TIM-1* is the most polymorphic in both mice and humans. In humans, *TIM-1* is extremely polymorphic, with single nucleotide polymorphisms (SNPs) as well as insertion/deletion variants in the mucin domain. Association studies were performed in sight of the significant polymorphic variants, and these studies demonstrated that certain polymorphic variants of *TIM-1* were associated with protection against atopic diseases.

The association between *TIM-1* and atopy and that *TIM-1* is an atopy susceptibility gene have been reproduced in a number of other populations, including African-American asthmatics, children with atopic dermatitis in Arizona, and Australia, Koreans with asthma and atopic dermatitis, but not in Japanese children with asthma. The reporting of no association between *TIM-1* and asthma in Japanese children may be implicated to a decreased incidence of HAV infection, which now is close to zero in young Japanese children (Rodriguez-Manzanet *et al.*, 2009).

In this study, we analyzed the association between the 2 promoter polymorphisms of

TIM-1, -416G > C and -1454G > A, and AR in Egyptian patients sensitized to house dust mites. Our results showed no significant association between these two polymorphisms and AR. These results come in contrast to Mou *et al.*, 2010 who found a significant association between the same 2 SNPs in *TIM-1* gene promoter (-416G>C, 1454G>A) and AR in patients of Han Chinese ethnicity.

Our results also do not agree with that of Liu *et al.*, 2007 whose results showed a significant association between the -416G > C polymorphism and asthma. They further examined the functional role of this promoter polymorphism, and found that the single base substitution at -416 impaired a functional promoter element and affected the transcriptional activity of the *TIM-1* gene. Mete *et al.*, 2014 study showed that *TIM1* -416G > C polymorphisms were significantly associated with asthma in Turkish patients. Wu *et al.*, 2009 observed, on the other hand, no association between another 2 *TIM-1* polymorphisms (-232 G > A and 5383_5397ins/del) and asthma susceptibility in middle China.

In conclusion, our results demonstrated that the genetic variation in the *TIM-1* gene promoter (-416G>C and 1454G>A) is not a possible risk factor for AR in Egyptian patients. Nevertheless, we do not exclude the possibility that other *TIM-1* polymorphisms might be associated with AR. Indeed, because of the limited number of our studied patients, we recommend that further studies are needed to further confirm the association between the 2 SNPs genotyped in this study and AR.

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