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Association of ADAM33 gene polymorphisms with allergic asthma

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ABSTRACT

Objective(s): Asthma results from the interaction between genetic and environmental factors. ADAM33 gene on chromosome 20p13 is associated with asthma and airway hyperresponsiveness.
Materials and Methods: This is a case-control study, where four SNPs S1 (rs3918396), T1 (rs2280091), T2 (rs2280090), V4 (rs2787094) of ADAM33 gene have been assessed in patients with allergic asthma and normal controls (95 patients and 86 normal). Blood samples of these participants have been genotyped by PCR and the RFLP method.
Results: There was no association between asthmatic patients and polymorphisms of alleles, genotypes and haplotypes of the ADAM33 gene. When categorizing the asthmatic patients in severe, moderate and mild groups, associations in the subcategories of asthmatic patients were found. There were associations between polymorphisms of C allele of T1 SNP with severe asthmatic patients and G allele of V4 SNP with moderate asthmatics respectively (P=0.006, P=0.01). There was a significant association between sensitivity to mite and polymorphism of C allele of T1 SNP (P=0.02). Besides, there was a significant association between sensitivity to weeds and genotype GG of V4 SNP (P=0.05).
Conclusion: Polymorphisms of ADAM33 gene might be associated with severe asthma and sensitivity to aeroallergens in northeast of Iran, but further studies are needed to determine the polymorphisms in this area and other regions of our country.

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Introduction

Asthma is a worldwide problem that is more common in developed countries. An estimated 300 million people worldwide are suffering from asthma. The prevalence of asthma in children and adults is 3 to 38 and 2 to 12 percent, respectively. Asthma affects 10% of people in Iran. In recent decades, the prevalence of asthma has increased especially in developed countries (1–3). Asthma is a chronic lung disease characterized by increased bronchial responsiveness, obstruction of the airways and pulmonary symptoms. In this disease, acute and chronic inflammation and tissue changes include a thickened airway, sub-epithelial fibrosis and increased smooth muscle mass. Although the majority of people who are suffering from asthma have normal lung function, accelerated loss of lung function can occur in some people (4–6). Asthma results from the interaction of genetic and environmental factors. 20p13 chromosome is associated with asthma and increased airway responsiveness. A disintegrin and metalloprotease domain 33 (ADAM33) gene in this chromosomal region is a candidate gene for asthma and increased bronchial responsiveness. This gene is one of the members of the metalloproteinase and disintegrin protein family that is classified as disintegrin and metalloproteina- ses (7). ADAM family includes three members with very complex structures. ADAM proteins are transmembrane proteins with multiple domains, which are involved in many cellular activities. ADAM family plays an important role in cell adhesion, proliferation, differentiation, signal transduction, apoptosis and inflammatory responses. This gene is expressed in lung fibroblasts and smooth muscle and it has been associated with increased bronchial

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Table 1. Features of SNP, primer sequence, length of PCR product and restriction enzyme

Name of SNP	Primer sequence	PCR product (b.p.)	Restriction enzyme
S1 (rs3918396)	Forward: 5′-TGTGCAGGCTGAAAGTATGC-3' Reverse: 5′-AGAGCTCTGAGGAGGGGAAC-3'	304	BtsCI
T1 (rs2280091)	Forward: 5'-ACTCAAGGTGACTGGGTGCT-3' Reverse: 5'-GAGGGCATGAGGCTCACTTG-3	400	NcoI (Bsp19I)
T2 (rs2280090)	Forward: 5'-TTCTCAGGGTCTGGGAGAAA-3' Reverse: 5'-GCCAACCTCCTGGACTCTTA-3'	310	HpyCH4III (TaaI)
V4 (rs2787094)	Forward: 5'-ACACACAGAATGGGGGAGAG-3' Reverse: 5'-CCAGAAGCAAAGGTCACACA-3'	374	PstI (BstMAI)

responsiveness (8–11). The present study was designed to investigate the association between four ADAM33 gene polymorphisms and allergic asthma by PCR-RLFP method.

Materials and Methods

Subjects

The participants, who were referred to Ghaem Hospital, filled out a questionnaire for identifying their signs and symptoms according to Global Initiative for Asthma (GINA) guidelines. After obtaining informed consent from the patients, spirometry was performed for each patient based on forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC) and the ratio FEV1/FVC in either normal situation or 10-15 min after exercise and/or bronchodilator administration. Skin allergy prick test was done for diagnosis of allergy in all participants. Allergen extracts used in the skin prick test included extracts of common allergens consisting of aeroallergens (pollens of trees, grasses and weeds) and dust mites. After providing an informed consent, the control group filled out a questionnaire. Then, clinical examination and the prick skin test were performed for allergic evaluations.

Genotyping

Five milliliters of venous blood obtained from each participant was collected in falcon containing EDTA. Genomic DNA was extracted using DNA extraction kit (Pars Toos,Iran). Using specific primers for the four SNP types (T1, T2, S1, and V4), PCR was performed, then, SNP types in amplified fragment were evaluated using restriction enzymes. Features of the SNPs, primers sequence, PCR product length and restriction enzymes are shown in Table 2.

Statistics

Frequency of allele and genotypes between case and control groups and individual subgroups were analyzed by X2 test. Statistical analysis was performed using the SPSS software (Version 16.0). The *P-values* equal to or less than 0.05 are considered as significant. Statistical analysis of haplotype was performed by "Epi. Info" software. The distribution of allele frequencies was tested for conformity to the Hardy-Weinberg equilibrium by the $\chi 2$ test. The degree of linkage disequilibrium between loci was measured using Lewontin's Dm.

Results

The mean ages of the asthma patients and the control group were 34 years (range, 7 to 64 years), and 29 years (range, 2 to 75 years), respectively. 66% of patients and 37% of the control subjects were female and 29 patients (30%) had a family history of asthma. In the case group, 75 (79%), 75(79%), 84 (88%), and 70 (74%) of patients were sensitive to the tree pollen, grass, weeds, and mite, respectively. The demographics of patients and genotype frequencies in the asthma and control groups are listed in Tables 2 and 3, respectively.

Characterization of alleles and genotypes of different types of phenotypes in patients with asthma is presented in Table 6. There was an association between polymorphism of C allele of T1 SNP with severe asthma (P=0.006). Also, a significant difference was found between G allele of V4 SNP with moderate asthmatics (P=0.01). There was no association between asthmatic patients and polymorphism of ADAM33 gene and other phenotypes.

Frequency of alleles and genotypes of four SNPs (S1, T1, T2, and V4) are presented in Table 4. There were no associations between alleles and genotypes of the four SNPs in the patient group when compared to the control group.

Different haplotypes of ADAM33 gene are presented in Table 5. There were no significant differences between 12 types of haplotypes in the two groups.

There was a significant association between sensitivity to mite and polymorphism of C allele of T1 SNP (P=0.02). Besides, there was a significant association between sensitivity to weeds and genotype GG of V4 SNP (P=0.05). There was no significant association among other alleles and genotypes as shown in Table 7.

Table 2. The Hardy–Weinberg equilibrium analysis for case and control

SNP genotypes types	HWE Con (*P-value*)	HWE Case (*P-value*)	HWE Case/Con (*P-value*)
S1	0.00	0.74	0.00
T1	0.35	0.72	0.89
T2	0.01	0.51	0.01
V2	0.99	0.94	0.96

Table 3. Demographic characterization of patients and control group

Variable	Control group (n=86)	Patients (n=95)
Sex:		
Male	49(57%)	42 (44%)
Female	37 (43%)	53 (56%)
Age (year):		
Minimum	2	7
Maximum	75	64
Intermediate	39	34
Maximum capacity of expiratory:		
Minimum	—	34%
Maximum	—	128%
Intermediate	—	81%
Maximum expiratory volume in 1st sec:		
Minimum		
Maximum	—	30%
Intermediate	—	124%
	—	78%
Severity of asthma:		
mild	—	52 (54%)
moderate	—	28 (30%)
severe	—	15 (15%)
Family history of asthma	—	29 (30%)
Prick skin test		
Tree pollen	—	75 (79%)
grass	—	75 (79%)
weeds	—	84 (88%)
mite	—	70 (74%)

Table 4. Frequency of alleles and genotypes of ADAM33 in patients with asthma and the control group

SNP	Allele & genotype	Case	Control	*P-value*	Odds ratio
S1	A	175 (92.1%)	160 (93%)	0.98	0.88
	G	15 (7.9%)	12 (7%)	0.99	1.00
	GA	14 (14.7%)	12 (14%)	0.98	1.00
	AA	81 (85.3%)	74 (86%)	0.95	0.95
T1	C	142 (74.7%)	144 (83.7%)	0.24	0.66
	T	48 (25.3%)	48 (16.3%)	0.54	1.11
	CT	32 (33.6%)	40 (46%)	0.30	0.81
	TT	7 (7.4%)	4 (5%)	0.92	1.02
	CC	56 (59%)	42 (49%)	0.39	1.19
T2	C	37 (19.5%)	41 (24%)	0.81	0.95
	T	153 (80.5%)	131 (76%)	0.65	1.21
	CT	34 (35.7%)	40 (47%)	0.34	0.82
	TT	59 (62%)	46 (53%)	0.38	1.23
	CC	2 (2.3%)	-------	-----	-----
V4	G	134 (70%)	129 (75%)	0.59	0.83
	C	56 (30%)	43 (25%)	0.74	1.07
	GG	47 (49%)	49 (57%)	0.47	0.84
	GC	38 (40%)	32 (37%)	0.85	1.05
	CC	9 (11%)	5 (6%)	0.76	1.05

Table 5. Frequency of haplotypes of ADAM33 in patients with asthma and the control group

Haplotype	Case	Control	*P-value*	Odds ratio
H1 (ATTG)	11(5.7%)	10 (5.8)	0.94	0.99
H2 (ATCC)	8 (4.2%)	11 (6.3%)	0.94	0.99
H3 (ACTG)	97 (51%)	93 (54%)	0.28	0.79
H4 (ATTC)	5 (2.6%)	5 (2.9%)	0.95	0.99
H5 (GCTC)	6 (3.1%)	8 (4.6%)	0.97	0.98
H6 (ACTC)	28(14.7%)	13(7.5%)	0.64	1.08
H7 (GCTG)	2 (1.01%)	2 (1.2%)	0.98	1.00
H8 (ACCG)	6 (3.1%)	4 (2.3%)	0.98	1.00
H9 (ATCG)	19 (10%)	20(11.6%)	0.96	0.98
H10(ACCC)	2 (1.05%)	4 (2.3%)	0.98	0.98
H11(GTCC)	1 (0.58%)	3 (1.5%)	0.99	0.99
H12(GTCG)	1 (1.05%)	1 (0.58%)	0.99	1.00

Table 6. Frequency of alleles and genotypes of ADAM33 in patients with asthma and the control group

Alele & genotype		**Control**	**Asthmatic patients**					
			Mild	*P-value*	Moderate	*P-value*	Severe	*P-value*
S1	A	160 (93%)	95 (91%)	0.86	52 (93%)	0.99	28 (93%)	0.79
	G	12 (7%)	9 (9%)	0.94	4 (7%)	0.94	2 (7%)	0.94
	AA	74 (86%)	43 (83%)	0.72	24 (86%)	0.85	13 (87%)	1.00
	GA	12 (14%)	9 (17%)	0.88	4 (14%)	0.94	2 (13%)	1.00
T1	C	144 (84%)	80 (77%)	0.33	44 (76%)	0.27	19 (63%)	0.006
	T	48 (16%)	24 (23%)	0.63	14 (24%)	0.58	11 (27%)	0.09
	CC	40 (46%)	30 (59%)	0.22	18 (64%)	0.07	5 (33%)	0.27
	TT	4 (5%)	3 (6%)	1.00	2 (8%)	0.88	1 (7%)	0.94
	CT	42 (49%)	18 (35%)	0.22	8 (28%)	0.07	9 (60%)	0.77
T2	C	41 (24%)	20 (19%)	0.75	9 (16%)	0.58	9 (30%)	0.68
	T	131 (76%)	84 (81%)	0.54	47 (84%	0.21	21 (70%)	0.49
	CT	41 (47%)	18 (35%)	0.31	9 (34%)	0.23	9 (38%)	0.45
	TT	45 (53%)	33 (63%)	0.22	19 (66%)	0.18	6 (24%)	0.38
	CC	------	1 (2%)	----	-------	------	------	------
V4	G	129 (75%)	76 (73%)	0.89	37 (54%)	0.01	21 (70%)	0.59
	C	43 (25%)	28 (27%)	0.93	32 (46%)	0.08	9 (30%)	0.74
	GG	49 (57%)	28 (54%)	0.83	11 (40%)	0.11	9 (60%)	0.74
	GC	32 (37%)	20 (38%)	1.00	15 (55%)	0.10	3 (20%)	0.18
	CC	5 (6%)	4 (8%)	0.94	2 (5%)	1.00	3 (20%)	0.32

Discussion

Van Eerdewegh reported that the ADAM33 gene is expressed restrictively in human fibroblasts and smooth muscles. ADAM33 polymorphism can accelerate proliferation in the smooth muscles and fibroblasts, which causes sub-epithelial fibrosis and increased bronchial responsiveness. ADAM33 gene, with specific polymorphisms increases shift toward inflammation or immune responses mediated by the T-helper 2 cell (11–13).

Several studies have found a significant difference in ADAM33 gene expression between the healthy and asthmatic subjects. For example, Van Eerdewegh observed a significant correlation between seven SNP alleles (F+1, Q-1, S1, S2, ST+4, V-1, and V4) in 421 families (6). Moreover, similar results were reported by Robby Benjamin in America, and by Jay H Lee and LG Bloki in Korea (7–9). In the present study the relationship among ADAM33 gene polymorphisms, the severity of asthma and allergic reactions was investigated. This case-control study was performed on 95 patients with allergic asthma and 86 cases of non-allergic healthy volunteers as a control group in the northeast of Iran, Mashhad. We evaluated the four SNPs that more studies have focused on. This investigation was done for the first time in Iran. Our results showed that there was no significant association between the asthma patients and the control group with regard to ADAM33 gene polymorphisms and haplotypes. In line with Elçin Bora in Turkey, Denise L. Lind in Puerto Rico, and Wang, P. Liu in China, we found no relationship between ADAM33 gene polymorphisms and asthma (14–16).

However, several studies have reported a signify-cant relationship between ADAM33 gene polymer-phisms, asthma, increased bronchial responsiveness to methacholine, restrictive abnormal airway and total serum IgE levels in America, England, Germany, China, Japan, South Korea, Latin America, India, Australia, Turkey and Saudi Arabia (17–30). In the present study, the asthmatic patients were divided into mild, moderate and severe groups based on the FEV1 value. Different types of patients were compared with the control group; significant differences in the T allele of SNP T1 were observed in patients with severe asthma.

Table 7. Investigation of gene polymorphism in patients with allergic asthma and the control group

SNP	Alleles & Genotypes	Control	Asthmatic Sensitive To Aeroallergens							
			Trees	*P*-value	Grss	*P*-value	Weeds	*P*-value	Mite	*P*-value
S1	A	160 (92%)	145 (92%)	0.80	144 (91%)	1.00	165 (92%)	0.80	126 (91%)	1.00
	G	12 (8%)	13 (8%)	0.94	14 (9%)	1.00	15 (8%)	0.94	12 (9%)	1.00
	AA	74 (86%)	66 (75%)	0.10	66 (81%)	0.48	76 (84%)	0.85	59 (38%)	0.72
	GA	12 (14%)	12 (25%)	0.43	13 (19%)	0.75	14 (16%)	0.94	12 (17%)	0.88
T1	C	124 (84%)	114 (73%)	0.12	118 (74%)	0.16	136 (74%)	0.16	109 (67%)	0.02
	T	48 (16%)	41 (27%)	0.42	42 (26%)	0.47	47 (26%)	0.47	55 (33%)	0.08
	CC	40 (46%)	45 (59%%)	0.22	46 (58%)	0.26	52 (56%)	0.36	43 (61%)	0.15
	TT	4 (5%)	7 (9%)	0.82	7 (9%)	0.82	7 (8%)	0.88	6 (8%)	0.88
	CT	42 (49%)	24 (32%)	0.14	26 (34%)	0.19	30 (36%)	0.26	21 (31%)	0.12
T2	C	41 (24%)	31 (20%)	0.75	31 (20%)	0.75	34 (19%)	0.75	26 (18%)	0.69
	T	131 (76%)	124 (80%)	0.65	126 (80%)	0.65	14 (81%)	0.54	114 (82%)	0.44
	CT	41 (47%%)	28 (36%)	0.35	28 (35%)	0.31	29 (33%)	0.27	23 (34%)	0.27
	TT	45 (53%)	48 (61%)	0.18	50 (62%)	0.28	56 (64%)	0.27	44 (65%)	0.22
	CC	---------	2 (3%)	------	2 (3%)	-----	2 (3%)	-----	1 (1%)	----
V4	G	129 (75%)	112 (73%)	0.89	115 (72%)	0.78	125 (73%)	0.89	101 (72%)	0.78
	C	43 (25%)	42 (37%)	0.93	44 (38%)	0.37	56 (27%)	0.93	39 (28%)	0.87
	GC	49 (57%)	30 (38%)	0.08	31 (40%)	0.11	35 (44%)	0.23	29 (44%)	0.50
	GG	32 (37%)	42 (54%%)	0.12	40 (52%)	0.18	44 (58%)	0.05	35 (53%)	0.15
	CC	5 (6%)	7 (8%)	0.94	6 (8%)	0.94	7 (8%)	0.94	2 (3%)	0.88

There was no genetic correlation in the remaining alleles, and no significant differences between values of alleles and genotypes in patients with asthma. Besides, there was a significant difference between values of the SNP T1 allele in patients with severe asthma compared to the control ones. It is highly probable that this association is more significant if a larger population is studied. Furthermore, it has been shown that there is an association between moderate asthma and the V4 polymorphism. On the other hand the Hardy–Weinberg equilibrium is present in this group. There was a relationship between allergic sensitivity to aeroallergens and ADAM33 gene polymorphism in patients suffering from asthma. Similar studies have investigated the association between gene polymorphism and total IgE levels, but a study using prick skin test is unprecedented in the literature. Hence, our study is the first to investigate the relationship between ADAM33 gene polymorphism and allergic sensitivity using the prick skin test. This study was done in the northeast of Iran; since Iran has diverse ethnic groups, it is suggested to perform similar studies on other populations. Polymorphisms of ADAM33 gene might be associated with severe asthma and sensitivity to aeroallergens.

Conclusion

Polymorphisms of ADAM33 gene might be associated with severe asthma and sensitivity to aeroallergens in the northeastern population of Iran. Further studies are needed in other districts of Khorasan and Iran.

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