



Short Communication

Frequency of genetic polymorphisms of ADAM33 and their association with allergic rhinitis among Jordanians



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ABSTRACT

Allergic rhinitis is a chronic inflammatory disease that is assumed to be due to an interaction between different genetic and/or environmental factors. A disintegrin and metalloprotease domain 33 (*ADAM33*) has been extensively studied as a susceptibility gene in asthma and has been linked to bronchial hyper-responsiveness. In this study, we investigated the association between *ADAM33* single nucleotide polymorphisms and the incidence of allergic rhinitis among the Jordanian population. We conducted a case–control association study on 120 adult individuals diagnosed with allergic rhinitis and 128 normal healthy controls. 8 single-nucleotide polymorphisms in *ADAM33* were genotyped using PCR-RFLP method. No significant differences in the allelic frequencies of all SNPs tested between AR patients and the control volunteers were found, although S2 C/G SNP showed a tendency toward significance with $P = 0.06$. On the genotype level significant association were found in the following genotypes: T1 AA, T1 AG, T2 GG, T2 AG, T + 1 GG, T + 1 AG, V4 CG, S2 CC, S2 CG, Q-1AA. Seven haplotypes were present only within AR patients and eight haplotypes were completely absent from the AR patients. Three haplotypes exhibited significant association with AR $P \leq 0.05$, two of them were present only in AR patients. In conclusion, the polymorphisms in the *ADAM33* gene are associated with susceptibility to AR in the Jordanian population. Furthermore, the haplotype of the tested SNPs were also associated with the risk of AR.

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1. Introduction

Allergic rhinitis (AR) is characterized by nasal discharge, blockage, sneezing, and itching (Anon, 2002). The incidence of allergic rhinitis (AR) is currently increasing worldwide. The morbidity of allergic rhinitis is estimated to be from 10 to 25% in different countries with a rough estimation of 15% in the Jordanian population, but no study has been carried out to assess the exact figures. AR is assumed to be due to an interaction between different genetic and/or environmental factors and involves the stimulation of the immune cells and the release of many pro-inflammatory mediators in allergen-sensitized individuals (Zhang et al., 2009). Allergy is identified with the type 1 hypersensitivity disorder, in which IgE plays an essential role. Some individuals appear to be genetically predisposed to produce more IgE in response to an allergen.

Abbreviations: *ADAM33*, A disintegrin and metalloprotease domain 33; AR, Allergic rhinitis; IgE, Immunoglobulin E; SNPs, Single nucleotide polymorphisms; JUH, Jordan University Hospital; IRB, Institutional Review Board; PCR/RFLP, Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; NCBI, National Center for Biotechnology Information.

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Studies have shown that condition such as asthma and allergic rhinitis is linked with increased IgE and determining IgE level is very helpful in the diagnosis of patients with established or suspected allergic diseases (Holt et al., 1999; Holgate, 1999). Both AR and asthma are characterized by a similar inflammatory process and may both be manifestations of the atopic syndrome (Grossman, 1997). Their inflammatory response share similar respiratory epithelial structure of ciliated pseudostratified columnar epithelium with goblet cells (Simons, 1999). Further pathophysiological similarities can be seen on the local mediator that is released by the immune system (Simons, 1999). The connection between AR and asthma were illustrated on the clinical level in many studies (Braunstaal et al., 2000; Braunstaal et al., 2001). Those studies compared allergic inflammation with clinical findings from the upper and lower airways after nasal allergen provocation and bronchial provocation (SBP) with an allergen and concluded that the response toward the challenge is similar in any part of the airways and leads to differentiation and migration of progenitors from the bone marrow, and directly or indirectly affects both upper and lower airway function (Braunstaal et al., 2000; Braunstaal et al., 2001 Mar). On the genetic level, there are some evidences that AR and asthma share a common genetic background (Grossman, 1997).

Table 1
Description of the investigated *ADAM33* SNPs.

SNP name	Reference SNP ID	Allele	Primers used in PCR	Restriction enzyme	Length of digested fragments (bp)
T1	rs2280091	A/G	[15]	NcoI	A: 140, 260 G: 400
T2	rs2280090	G/A	[15]	HpyCH4III	G: 310 A: 198, 112
S1	rs3918396	G/A	[15]	SfaNI	G: 196, 108 A: 140, 108, 56
S2	rs528557	G/C	[17]	KasI	G: 289 C: 158, 131
V4	rs2787094	C/G	[15]	PstI	C: 206, 168 G: 374
F + 1	rs511898	C/T	[18]	BsmBI	C: 206, 166 T: 372
Q-1	rs612709	G/A	F-5'-GCTCCTGGAAGGCATTCTT-3' R-5'-GTTACCTAGATGCCAGGA-3'	BseRI	G: 244 A: 118, 126
T + 1	rs2280089	G/A	F-5'-CTGAGCCCGAAACCTGATT-3' R-5'-GATCACTGTGCCAACCTCT-3'	MboII	G: 483 A: 292, 191

A disintegrin and metalloprotease domain 33 (*ADAM33*), a gene located on chromosome 20p13 and a member of the ADAM family, has been extensively studied as a susceptibility gene in asthma and has been linked to bronchial hyper-responsiveness (Howard et al., 2003). Studies found that the SNPs in *ADAM33* are involved in the development of lung dysfunction (Wang et al., 2009). It has been illustrated that the alteration of this protein function might be involved in the airway remodeling as *ADAM33* is expressed in the smooth muscle, myofibroblasts, and fibroblasts of asthmatic airways (Jongepier et al., 2004). Van Eerdewegh et al. (2002) have also shown that the linkage of *ADAM33* gene to asthma was strongly correlated with BHR. Moreover *ADAM33* has been shown to have a role in altering the growth factor expression, and in the regulation immune response mediated by Th2 cells (Van Eerdewegh et al., 2002).

In four unique asthma populations including the African American, the US white, the US Hispanic and the Dutch, the association of *ADAM33* polymorphisms with asthma and related phenotypes has been replicated (Howard et al., 2003). However, this association was not found in the Puerto Rican and Mexican populations (Lind et al., 2003). The association between AR and *ADAM33* was also confirmed in two studies conducted on the Chinese and the Japanese population (Cheng et al., 2004; Su et al., 2008). In the Japanese study, the author illustrated that six SNPs of *ADAM33* gene, three in introns and three in the coding region, are strongly associated with allergic rhinitis due to

Table 2
Characteristics of studied population.

Phenotype	Sample size	% Females % males	Av. age ± SD	P-value* T-test	Mean IgE-level ± SD	P-value* T-test
AR	120	0.61 0.39	30.90 ± 12.8	≤0.05	71.1 ± 140	≤0.05
Control	128	0.48 0.52	35.14 ± 16.7		17.8 ± 23.4	

* Significant at $P \leq 0.05$.**Table 3**
Minor allele frequencies of eight SNPs in *ADAM33* and their association analyses.

SNP name	Nucleotide change	Total frequency	Frequency in control	Frequency in rhinitis	Minor allelic association with rhinitis χ^2 (P-value)*	HWE exact p
T1	A/G	0.21	0.18	0.25	1.45 (0.23)	0.71
T2	G/A	0.22	0.19	0.25	1.05 (0.31)	0.58
T + 1	G/A	0.21	0.18	0.25	1.45 (0.23)	0.70
V4	C/G	0.2	0.18	0.22	0.5 (0.48)	0.70
S1	G/A	0.05	0.05	0.06	0.096 (0.76)	1
S2	C/G	0.38	0.32	0.45	3.57 (0.06)	0.79
F + 1	T/C	0.39	0.35	0.43	1.35 (0.25)	0.69
Q-1	G/A	0.16	0.13	0.19	1.34 (0.25)	0.35

* Significant at $P \leq 0.05$.

Japanese cedar pollen (Cheng et al., 2004; Su et al., 2008). Moreover, the author showed that most of the SNPs were in linkage disequilibrium with each other. In the Chinese study, the author showed that single nucleotide polymorphisms of the *ADAM33* gene may modify individual susceptibility to AR (Su et al., 2008). The aim of the present study was to determine whether *ADAM33* SNPs are associated with AR among the Jordanian population. The chosen SNPs were previously associated with the susceptibility of asthma and/or AR in different populations (Cheng et al., 2004; Su et al., 2008; Anon, September 15–19 2007).

2. Material and methods

2.1. Study population

This case–control study included 120 allergic rhinitis patients (AR) and 128 healthy controls. They were recruited for the study between August 2011 and October 2012, at Jordan University Hospital (JUH), Amman, Jordan. The study protocol was approved from the institutional review board (IRB) of the University of Jordan. The diagnosis of allergic rhinitis was according to the treating physician based on history, physical examination and was confirmed by skin prick test of the patients. Exclusion criteria were a present or past history of asthma and asthma-like symptoms. None of the patients had received specific immunotherapy for allergic conditions. The control subjects were all symptom free, had no history of atopic disorders, and had normal IgE level. All patients and control subjects have signed an informed consent.

2.2. Total IgE level measurement

Serum total IgE levels were measured for all participants using Total IgE ELISA kit (IBL international, GMBH, Hamburg, Germany). The results were read using ELISA Reader. According to the kit ranges, an IgE level below 100 IU/mL is considered normal.

2.3. DNA isolation

Venous blood samples (5 ml) were collected in EDTA tubes. Genomic DNA was extracted using Wizard Genomic DNA Purification Kit (Promega, USA). Isolated DNA was stored at -20°C till use.

2.4. Genotyping of *ADAM33* gene by PCR-RFLP

The genetic polymorphism analysis of 8 SNPs for *ADAM33* gene was determined by polymerase chain reaction/restriction fragment length polymorphism (PCR/RFLP) method. The SNP names, primers and restriction enzymes used are described in Table 1. The PCR products were digested overnight by restriction endonuclease and were thereafter separated by electrophoresis on agarose gel and stained with ethidium bromide. The SNP designations used in this study were according to the SNPs database within NCBI.

Table 4
Pairwise linkage disequilibria (D') of ADAM33 eight SNPs.

	T2	T + 1	S1	S2	V4	F + 1	Q-1
T1	0.988	0.976	0.867	0.995	0.963	0.867	0.699
T2		0.988	0.874	0.995	0.928	0.872	0.726
T + 1			0.877	0.995	0.981	0.867	0.597
S1				0.608	0.117	0.035	0.167
S2					0.998	0.998	0.999
V4						0.848	0.920
F + 1							0.947
Q-1							

2.5. Statistical analysis

SNP and haplotype frequencies across rhinitis and controls were computed using ordinal logistic regression analysis as implemented in SNPStats (Sole et al., 2006). Linkage disequilibrium among the eight SNPs was calculated as D' (20). D' is the linkage disequilibrium coefficient standardized by the maximum value. The significant departure from the Hardy–Weinberg equilibrium (HWE) was assessed by the procedure described in (Guo and Thompson, 1992) using a test analogous to Fisher's exact test as implemented in ARLEQUIN (Excoffier et al., 2005). Analysis of association for each SNP with rhinitis and each haplotype with rhinitis were computed using the web tool SNPStats. P-value was adjusted as significant when $P \leq 0.05$. The statistical analyses are performed in a batch call to the R package (R Development Core Team, 2005, <http://www.R-project.org>).

3. Results

The 120 AR cases were aged from 11 to 61 years with a median age of 30.9 ± 12.8 years including 73 females (61%) and 47 males (39%). The 128 control subjects collected were aged from 5 to 73 years with a median age of 35.14 ± 16.7 years including 62 females (48%) and 66 males (52%). T-test and Chi-square test showed significant differences between rhinitis patients and control group for age $P \leq 0.05$ and gender ($P \leq 0.05$), respectively (Table 2). A significant difference in serum total IgE level was found between AR patients and controls

with mean (range) of total IgE levels of 71.1 ± 140 (0.8–991) IU/mL and 17.8 ± 23.4 (0.8–140) IU/mL, respectively ($P \leq 0.05$) (Table 2). Further statistical analysis was corrected toward those two confounders.

The allele frequencies of the ADAM33 gene polymorphisms in patients and healthy controls are shown in Table 3. The total allele frequencies for the eight SNPs ranged between 0.16 and 0.39. However, for the healthy alone it was between 0.05 and 0.35 and for the rhinitis between 0. and 0.45 (Table 3). All SNPs were in HWE as the null hypothesis for departure from HWE was rejected for all SNPs (Table 3). No significant differences in the allelic frequencies of all SNPs tested between AR patients and the control volunteers were found, although S2 C/G SNP showed a tendency toward significance with $P = 0.06$. The linkage disequilibrium between the tested SNPs were tested and all SNPs were found to be highly linked except S1 with F + 1 as the D' is 0.035 (Table 4). On the genotype level, significant associations were found in the following genotypes: T1 AA, T1 AG, T2 GG, T2 AG, T + 1 GG, T + 1 AG, V4 CG, S2 CC, S2 CG, Q-1AA (Table 5). The strongest association was found in S2 wild type genotype ($P = 0.002$) as 60 subjects in the control have the CC wild type allele; while only 33 on the patient side carried the CC wild type allele. V4 heterozygous allele ($P = 0.02$) and Q-1 AA minor allele ($P = 0.02$) also showed a strong association although to a lesser extent to S2 CC wild type allele (Table 5). In terms of haplotypes: 25 haplotypes resulted when combining the 8 SNPs. The order of SNPs in each haplotype from left to right was: T1, T2, T + 1, V4, S1, S2, F + 1, Q-1". Seven haplotypes were present only within AR patients and eight haplotypes were completely absent from the AR patients (Table 6). Three haplotypes exhibited significant association with AR $P \leq 0.05$, two of them were present only in AR patients and represent very strong association with P value of <0.0001 (Table 6).

4. Discussion

Many studies have focused on the role of ADAM33 polymorphism and the susceptibility to bronchial asthma (3 and 4), but not much has been done on AR patients. A recent meta-analysis has shown that polymorphisms in ADAM33 gene are risk factors for bronchial asthma (Liang et al., 2013). Importantly, this meta-analysis revealed a profound interethnic variation; as it illustrated that ADAM33 and risk of bronchial

Table 5
Genotype frequency distribution and association study in ADAM33 between rhinitis and control.

Genotype		Frequency: no. (%)		χ^2 (P- value)	Odds ratio (95% CI) crude analysis	Odds ratio (95% CI) adjusted by sex and age
		Control (n = 128)	Rhinitis (n = 120)			
T1	AA	86 (67.2)	66 (55)	3.88 (0.05) *	1.00 (ref)	1.00 (ref)
	AG	37 (28.9)	49 (40.8)	3.90 (0.05) *	1.73 (1.01–2.94)	2.11 (0.99–4.48)
	GG	5 (3.9)	5 (4.2)	0.01 (0.92)	1.3 (0.36–4.69)	3.82 (0.3–48.61)
T2	GG	84 (65.6)	64 (53.3)	3.89 (0.05) *	1.00 (ref)	1.00 (ref)
	AG	39 (30.5)	51 (42.5)	3.88 (0.05) *	1.72 (1.01–2.91)	2.25 (1.07–4.74)
	AA	5 (3.9)	5 (4.2)	0.01 (0.92)	1.31 (0.36–4.73)	4.12 (0.32–53.82)
T + 1	GG	86 (67.2)	66 (55)	3.88 (0.05) *	1.00 (ref)	1.00 (ref)
	AG	37 (28.9)	49 (40.8)	3.90 (0.05) *	1.73 (1.01–2.94)	1.98 (0.94–4.17)
	AA	5 (3.9)	5 (4.2)	0.01 (0.92)	1.3 (0.36–4.69)	3.76 (0.3–47.65)
V4	CC	89 (69.5)	70 (58.3)	3.38 (0.07)	1.00 (ref)	1.00 (ref)
	CG	32 (25)	46 (38.3)	5.11 (0.02) *	1.83 (1.06–3.17)	2.17 (1–4.72)
	GG	7 (5.5)	4 (3.3)	0.67 (0.41)	0.73 (0.20–2.58)	0.61 (0.07–5.63)
S1	GG	116 (90.6)	106 (88.3)	0.35 (0.56)	1.00 (ref)	1.00 (ref)
	GA	12 (9.4)	14 (11.7)	0.35 (0.56)	1.28 (0.57–2.88)	1.28 (0.41–3.98)
	CC	60 (46.9)	33 (27.5)	9.92 (0.002) *	1.00 (ref)	1.00 (ref)
S2	CG	53 (41.4)	67 (55.8)	5.16 (0.02) *	2.3 (1.32–4.01)	1.79 (0.79–4.07)
	GG	15 (11.7)	20 (16.7)	1.25 (0.26)	2.42 (1.10–5.36)	2.84 (0.88–9.15)
	TT	56 (43.8)	39 (32.5)	3.32 (0.07) *	1.00 (ref)	1.00 (ref)
F + 1	TC	55 (43)	59 (49.2)	0.96 (0.33)	1.54 (0.89–2.67)	1.36 (0.59–3.12)
	CC	17 (13.3)	22 (18.3)	1.19 (0.27)	1.86 (0.87–3.95)	2.26 (0.75–6.77)
	GG	96 (75)	82 (68.3)	1.36 (0.24)	1.00 (ref)	1.00 (ref)
Q-1	GA	31 (24.2)	31 (25.8)	0.09 (0.77)	1.17 (0.66–2.09)	0.76 (0.33–1.74)
	AA	1 (0.8)	7 (5.8)	5.06 (0.02) *	8.2 (0.99–68.00)	8.96 (0.5–160.2)

* Significant at $P \leq 0.05$.

Table 6
Haplotype frequencies and their association with rhinitis.

Haplotype	Frequency in all samples	Frequency in control	Frequency in rhinitis	P-value for the haplotypes associated with rhinitis
AGGCGCTG	0.4504	0.4963	0.4001	0.02*
GAACGGCG	0.1841	0.1573	0.2099	0.5
AGGGGCTG	0.1237	0.1278	0.1201	0.18
AGGCGGCA	0.0762	0.0684	0.0891	0.53
AGGGAGCA	0.0359	0.0303	0.0384	0.5
AGGCGCCG	0.0165	0.0287	0	–
AGGCAGCA	0.0165	0.0166	0.02	0.5
GAACGGTG	0.0138	0.0185	0.006	0.57
AGGGGGCA	0.0137	0	0.0233	<0.0001*
AGGCGGTG	0.0119	0	0.0291	<0.0001*
AGGGGCCG	0.0101	0.0112	0.0127	0.65
AAGCGCCG	0.0081	0.0053	0.0083	–
AGGGGGTG	0.0064	0.0039	0.0047	–
AGGCGGCG	0.0061	0.0117	0	–
GAAGGGCG	0.0056	0	0.015	–
GAACGGCA	0.0041	0	0.0083	–
AGGCGGTA	0.0027	0.0058	0	–
AGGCGCTA	0.0021	0	0.0042	–
GAAGGCTG	0.0021	0	0.0045	–
AGGGGCCA	0.002	0	0.0043	–
AGACGGCA	0.002	0.0039	0	–
GAGGGGCG	0.002	0.0039	0	–
AAACGGCG	0.002	0.0039	0	–
GGGCGCCA	0.002	0.0039	0	–
AAGGGCCG	0	0.0026	0	–

Haplotype sequence as: T1, T2, T + 1, V4, S1, S2, F + 1, Q-1.

* Significant at $P \leq 0.05$.

asthma were more significant in the Asian population. Studies also have shown that AR and asthma are closely linked and the concept of “one airway, one disease” has emerged (Anon, 2007). Moreover, an association between AR and the polymorphisms in *ADAM33* were confirmed in the Chinese and the Japanese populations (Cheng et al., 2004; Su et al., 2008). In this context, we genotyped 8 SNPs in *ADAM33* gene to evaluate the potential role of *ADAM33* polymorphisms on AR risk among Jordanians.

In the single-locus analyses of AR risk, the allele frequencies of the 8 SNPs were not significantly different between the AR and control subjects ($P > 0.05$). Interestingly, S2 SNP showed a tendency toward significance with $P = 0.06$. The allele frequency of S2 was found to be significantly associated with allergic rhinitis in the Japanese population (Cheng et al., 2004). On the genotype site, the T1, T2, T + 1, V4, S2 heterozygote genotype and the Q-1 homozygote minor genotype were significantly higher in the AR patients than in the control volunteers ($P = 0.05, 0.05, 0.05, 0.02, 0.02, 0.02$, respectively). Importantly, five of these genotypes (T1, T2, T + 1, V4, S2) have been associated with AR in the Chinese study and four of these genotypes (T1, T2, T + 1, V4) were also linked to the Japanese allergic rhinitis incidence study. In the case of the Q-1 AA genotype, this is the first report to find a significant association with the risk of AR as it was not included in the Japanese study and was not detected in any of the patients nor the volunteers in the Chinese study (Cheng et al., 2004; Su et al., 2008). On the other hand, The homozygote common alleles were found to be significantly higher in the control volunteers than in the AR patients at T1, T2, T + 1, S2 SNPs ($P = 0.05, 0.05, 0.05, 0.002$). For the first three SNPs T1, T2, and T + 1 similar findings were reported in the Chinese study (Su et al., 2008). Importantly the meta-analysis results conducted by Liang et al. 2013 regarding the role of *ADAM33* gene polymorphism and risk of asthma are in support of our results as the author concluded that T1, T2, T + 1, V4 SNPs were associated with risk of asthma especially in the Asian population (Liang et al., 2013).

We have also observed a very close distribution of T1, T2, and T + 1 SNPs, and it seems that T1, T2, and T + 1 are in tight linkage disequilibrium in our population as shown in the linkage disequilibrium analysis. T1 and T2 polymorphisms are located in exon 19 and have been shown to affect the signal transduction as they affect the phosphorylation of

the cytoplasmic tail and an SH3 domain of *ADAM33* protein. S2 a synonymous SNP that is in tight link disequilibrium with other SNPs in *ADAM33* has been shown to affect the function of the lung (Anon, 2007). V4 SNP is located in the 3'UTR of *ADAM33* gene and suspected to have an effect on the transcription of *ADAM33* gene (van Diemen et al., 2005). Interestingly the homozygote minor allele patients have 8 times more risk to have AR (Adjusted OR ratio = 8.96). Q-1 SNP is in the intrinsic regions and studies suspect that Q-1 may influence the splicing of *ADAM33* to produce a variant protein (van Diemen et al., 2005). As multiple SNPs may increase the risk for AR, 8 haplotypes were constructed and significant differences were still observed and three haplotypes (AGGCGCTG, AGGGGGCA, AGGCGGTG) were found to be significantly higher in the AR patients. Taken together, despite the relatively small sample size in this study, these findings illustrate a clear evidence for the involvement of *ADAM33* gene in the pathophysiology of AR among Jordanians.

Combining the studies that illustrate the involvement of *ADAM33* in the development of lung dysfunction and the fact that upper and lower airways show similar inflammatory reactions to irritants and allergens together raise an important question whether *ADAM33* protein has a similar function in AR. Another potential explanation for the involvement of *ADAM33* in AR has been proposed by Miyake et al. (2012) after their positive results that showed a strong association between *ADAM33* genetic polymorphisms and rhino conjunctivitis in Japanese women (Miyake et al., 2012). They suggested the involvement of *ADAM33* protein in the angiogenesis process as *ADAM33* protein has a catalytic domain that causes rapid induction of endothelial cell differentiation *in vitro* and angiogenesis both *ex vivo* and *in vivo* (Puxeddu et al., 2008). The importance of airway angiogenesis in the pathophysiology AR has been illustrated by Kristan et al. (Kristan et al., 2009) as they have shown a significant elevation in the concentrations of angiogenesis-related factors such as angiogenin, vascular endothelial growth factor, and tumor necrosis factor- α in the sputum supernatant of patients with rhinitis without concomitant asthma compared to the healthy control group.

In conclusion, the findings of this study illustrated a strong association between 8 SNPs in *ADAM33* gene and incidence of allergic rhinitis among Jordanians. This association agrees with the already reported association between *ADAM33* polymorphism and allergic rhinitis in the Japanese and Chinese populations. Further, the findings agree with some of the meta-analysis conclusions conducted by Liang et al. (2013) that addressed the role of *ADAM33* gene polymorphism in asthma, which may indicate a close role for *ADAM33* in the incidence of asthma and allergic rhinitis. Moreover, the haplotypes of the tested SNPs were also strongly associated with the incidence of allergic rhinitis. However, more mechanism studies are needed to clarify the role of *ADAM33* in the pathophysiology of AR.

Conflict of interest

There is no conflict of interest.

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