



Contents lists available at SciVerse ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Short Communication

Association between ADAM33 S2 and ST+4 polymorphisms and susceptibility to asthma: A meta-analysis

Gwan Gyu Song, Jae-Hoon Kim, Young Ho Lee *

Division of Rheumatology, Department of Internal Medicine, Korea University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:

Accepted 1 April 2013

Available online xxxx

Keywords:

Asthma

ADAM33

Polymorphism

Meta-analysis

ABSTRACT

Objective: The aim of this study was to determine whether ADAM33 (a disintegrin and metalloproteinase domain 33) polymorphisms confer susceptibility to asthma in different populations.

Methods: We performed a meta-analysis on the association between the ADAM33 S2, ST+4, F+1, S1, and V4 polymorphisms and asthma.

Results: Thirteen studies in ten reports, which included 4942 patients and 7933 controls, were available for the meta-analysis. Meta-analysis stratified by ethnicity indicated an association between the ADAM33 S2 2 allele and asthma in Europeans (OR = 0.912, 95% CI = 0.851–0.977, $p = 0.009$). Meta-analysis revealed an association between asthma and the ADAM33 ST+4 2 allele (OR = 0.783, 95% CI = 0.762–0.999, $p = 0.048$). Stratification by ethnicity indicated an association between the ADAM33 ST+4 polymorphism and asthma in Asians. Stratification by age indicated an association between the ADAM33 ST+4 2 allele and asthma in adults (OR = 0.863, 95% CI = 0.782–0.964, $p = 0.008$). However, no association was found between asthma and the ADAM33 F+1, S1, and V4 polymorphisms.

Conclusions: This meta-analysis demonstrates that the ADAM33 S2 polymorphism confers susceptibility to asthma in Europeans and the ADAM33 ST+4 polymorphism is associated with asthma in Asians and adults.

© 2013 Published by Elsevier B.V.

1. Introduction

Asthma is an inflammatory disease characterized by intermittent inflammation of the small airways with symptoms of wheezing and shortness of breath. This inflammation leads to airway scarring and intractable airflow limitations. Although the etiology of asthma has not been determined, genetic studies have established that asthma susceptibility has a genetic component (Li et al., 2010).

ADAM33 (a disintegrin and metalloproteinase domain 33), located on chromosome 20p13, was the first gene identified in asthma by positional cloning (Van Eerdewegh et al., 2002). ADAM33 is a member of the multifunctional ADAM family of genes that code for zinc-dependent metalloproteinases. The ADAM33 protein has several domains, including metalloprotease-like, disintegrin-like, cysteine-rich, epidermal growth factor-like, transmembrane, and cytoplasmic domains (Yoshinaka et al., 2002). This protein is important for cell fusion, cell adhesion, cell signaling, and proteolysis and has been suggested to play an important role

in the activation of growth factors and Th2 cytokines (Shapiro and Owen, 2002). ADAM33 mRNA expression was found to be elevated in the lungs of a murine model of allergen-induced chronic airway inflammation (Jie et al., 2009) and in lung fibroblasts and bronchial smooth muscle. Furthermore, increased levels of ADAM33 mRNA and protein were detected in the bronchoalveolar lavage fluid and bronchial biopsies of asthma patients (Garlisi et al., 2003; Van Eerdewegh et al., 2002). These findings suggest that ADAM33 may be involved in the pathogenesis of asthma.

ADAM33 is highly polymorphic and several of its polymorphisms have been studied in asthma (Chae et al., 2003). However, whereas some reports have associated ADAM33 polymorphisms with asthma, others have found no association (Bijanazadeh et al., 2010; Blakey et al., 2009; Hirota et al., 2006; Howard et al., 2003; Jie et al., 2011; Lee et al., 2004; Qu et al., 2011; Su et al., 2008). This disparity may be due to small sample sizes, low statistical power, and/or clinical heterogeneity. Therefore, to overcome the limitations of individual studies, resolve inconsistencies, and reduce the likelihood of random errors causing false-positive or false-negative associations, we turned to meta-analysis (Lee et al., 2006a, 2006b). A recent review article by Sharma et al. showed that 17 ADAM33 polymorphisms have been done worldwide in case-control study settings (Sharma et al., 2011). The numbers of studies on the ADAM33 polymorphisms were various and some polymorphisms were not possible for meta-analysis due to the limited data. We selected 5 ADAM33 polymorphisms for meta-analysis based on the number of studies published. The aim of the present study

Abbreviations: ADAM33, a disintegrin and metalloproteinase domain 33; ORs, odds ratios; CIs, confidence intervals; H-W, Hardy-Weinberg; F, fixed effects model; R, random effects model.

* Corresponding author at: Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 126-1, Anam-dong 5-ga, Seongbuk-gu, Seoul 136-705, Republic of Korea. Tel.: +82 2 920 5645; fax: +82 2 922 5974.

E-mail address: lyhghg@korea.ac.kr (Y.H. Lee).

was to use meta-analysis to determine whether the ADAM33 S2, ST+4, F+1, S1, and V4 polymorphisms confer susceptibility to asthma.

2. Methods

2.1. Identification of eligible reports and data extraction

We performed a literature search using the MEDLINE citation database to identify articles that examined associations between the ADAM33 S2, ST+4, F+1, S1, and V4 polymorphisms and asthma. Combinations of keywords, such as 'ADAM33,' 'polymorphism,' and 'asthma' were entered as the Medical Subject Heading (MeSH) and text words. References in the identified reports were also used to identify additional reports not indexed by MEDLINE. Reports were included in this meta-analysis if (1) they were published before March 2012 (2) they contained original data (to ensure independence among studies), (3) they provided sufficient genotype data to calculate an odds ratio (OR), and (4) they showed how asthma was diagnosed in each study. The following were excluded: (1) reports containing overlapping data, (2) reports in which the number of null and wild genotypes could not be ascertained, (3) reports in which genotype distributions in the control population were not in accord with Hardy–Weinberg (H–W) expectations, and (4) reports in which family members had been studied, such as those involving transmission disequilibrium studies (because such analyses were based on linkage considerations). The following information was extracted from each report: author, year of publication, ethnicity of the study population, demographics, age, and number of cases and controls for each of the three polymorphisms. Allele frequencies were calculated from the corresponding genotype distributions.

2.2. Evaluation of publication bias

Funnel plots are often used to detect publication bias, but funnel plotting requires a range of studies of varying sizes involving subjective judgments. Therefore, we evaluated publication bias using Egger's linear regression test (Egger et al., 1997), which measures funnel plot asymmetry using a natural logarithm scale of odds ratios (ORs).

2.3. Evaluations of statistical associations

The chi-squared test was used to determine whether observed genotype frequencies conformed to H–W expectations (<http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>). We examined the contrast of the allelic effect of 2 (minor allele) versus 1 (common allele)

of ADAM33 polymorphisms. If an allelic association of the polymorphisms was found, further meta-analyses were performed using (1) co-dominant (2) recessive, and (3) dominant models. Subgroup analyses were performed by ethnicity and age. Point estimates of risks, ORs, and 95% confidence intervals (CIs) were calculated for each study. Cochran's Q-statistic was used to assess within- and between-study variations and heterogeneities. This heterogeneity test assesses the null hypothesis that all studies evaluated have the same effect. I^2 values were used to quantify heterogeneity. I^2 values range between 0% and 100% and represent the proportion of between-study variability that can be attributed to heterogeneity rather than chance (Higgins and Thompson, 2002). I^2 values of 25%, 50%, and 75% were nominally assigned as low, moderate, and high estimates, respectively. Larger samples yield more precise estimates than smaller samples. We adjusted sample sizes. Studies with larger samples were assigned more weight in the meta-analysis. The fixed effects model assumes that a genetic factor has the same effect on asthma susceptibility across all studies investigated, and that variations between studies are caused by chance alone. The random effects model assumes that different studies have substantial diversity and assesses within-study sampling errors and between-study variances. When study groups are homogeneous, the two models are similar, but when they are not, the random effects model usually provides wider CIs than the fixed effects model. The random effects model is used when there is significant heterogeneity between studies (DerSimonian and Laird, 1986). Statistical manipulations were undertaken using the Comprehensive Meta-Analysis computer program (Biostat, Englewood, NJ, USA). We conducted five types of meta-analyses, namely, on S2, ST+4, F+1, S1, and V4 polymorphisms of ADAM33 in asthma.

3. Results

3.1. Reports included in the meta-analysis

Seventy-four reports were identified by electronic and manual searches and 23 were selected for full-text review based on title and abstract details (Awasthi et al., 2011; Bijanzadeh et al., 2010; Blakey et al., 2009; de Faria et al., 2008; Hirota et al., 2006; Howard et al., 2003; Jie et al., 2011; Kedda et al., 2006; Lee et al., 2004; Lind et al., 2003; Noguchi et al., 2006; Qu et al., 2011; Raby et al., 2004; Schedel et al., 2006; Su et al., 2008; Tripathi et al., 2011; Undarmaa et al., 2010; Vergara et al., 2010; Wang et al., 2006; Werner et al., 2004; Zhang et al., 2009). Thirteen were excluded because they had no genotype data (Kedda et al., 2006; Lind et al., 2003; Raby et al., 2004; Schedel et al., 2006; Undarmaa et al., 2010; Vergara et al., 2010; Werner et al., 2004), they had no family data (Noguchi et al., 2006), or they had duplicate data (Zhang et al.,

Table 1
Characteristics of reports included in the meta-analysis.

Ref.	Ethnicity	Subject age	Subjects		Polymorphisms studied	Association findings	Diagnostic criteria
			Asthma	Control			
Jie et al. (2011)	Asian	Mixed	150	74	F+1, ST+4, S1, S2	F+1 ($p = 0.031$), ST+4, S1, S2 (NS)	Global Initiative for Asthma (GINA)
Qu et al. (2011)	Asian	Children	412	397	F+1, V4	F+1 (NS), V4 ($p < 0.001$)	Chinese Society of Respiratory Disease
Tripathi et al. (2011)	Asian	Adult	175	253	F+1, ST+4, S2, V4	F+1 ($p < 0.001$), ST+4 ($p = 0.013$), S2 ($p < 0.0001$), V4 ($p < 0.001$)	GINA
Awasthi et al. (2011)	Asian	Children	211	137	F+1, ST+4, S2, V4	F+1 ($p < 0.001$), ST+4 ($p = 0.010$), S2 ($p < 0.001$), V4 ($p = 0.031$)	GINA
Blakey et al. (2009)	European	Mixed	2021	5100	F+1, S2	F+1 (NS), S2 ($p = 0.032$)	Interview, questionnaires
Su et al. (2008)	Asian	Adult	181	151	V4, S1	V4($p < 0.0001$), S1 (NS)	Chinese Society of Allergology
Wang et al. (2006)	Asian	Adult	296	270	F+1	F+1 (NS)	
Hirota et al. (2006)	Asian	Adult	503	648	F+1, ST+4, S2, V4	F+1 (NS), ST+4 (NS), S2 ($p = 0.028$), V4 (NS)	American Thoracic Society
Lee et al. (2004)	Asian	Mixed	326	151	V4, S1	V4(NS) S1 (NS)	American Thoracic Society
Howard et al. (2003)	European	Adult	180	133	ST+4, S1, S2, ST+4	ST+4, S1, S2 (NS)	American Thoracic Society
	African	Adult	160	263	S1, S2, V4	S2 ($p = 0.03$), others (NS)	
	European	Adult	216	229	ST+4, S1, S2	ST+4, S1, S2 (NS)	
	Hispanic	Adult	111	127	S1, S2, V4	S2 ($p = 0.04$), others (NS)	

Ref. = reference, NS = not significant.

Table 2

Analysis of the association between the ADAM33 S2 polymorphism and asthma.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-Value	Model	p-Value	I ²
S2 2 vs. 1	Overall	9	1.522	0.921–2.515	0.101	R	0.000	97.3
	European	3	0.912	0.851–0.977	0.009	F	0.425	0
	Asian	4	2.467	0.669–9.104	0.175	R	0.000	98.6
	Adult	6	1.429	0.684–2.986	0.342	R	0.000	97.1
22 vs. 21 + 11 (recessive)	Overall	9	1.650	0.787–3.460	0.185	R	0.000	94.3
	European	3	0.789	0.664–0.937	0.007	F	0.192	0
	Asian	4	3.435	0.686–17.19	0.133	R	0.000	95.5
	Adult	6	1.493	0.557–4.005	0.426	R	0.000	93.2
22 + 21 vs. 11 (dominant)	Overall	9	1.658	0.982–2.798	0.058	R	0.000	95.4
	European	3	0.919	0.844–1.002	0.055	F	0.306	15.4
	Asian	4	3.148	0.639–15.49	0.159	R	0.000	97.9
	Adult	6	1.501	0.680–3.314	0.314	R	0.000	95.1
22 vs. 11 (codominant)	Overall	9	2.034	0.745–5.550	0.166	R	0.000	95.9
	European	3	0.769	0.645–0.917	0.004	F	0.669	0
	Asian	4	5.724	0.534–61.37	0.149	R	0.000	97.3
	Adult	6	1.706	0.434–6.705	0.445	R	0.000	95.2
22 vs. 21 (codominant)	Overall	9	1.425	0.825–2.460	0.204	R	0.000	87.8
	European	3	0.816	0.681–0.976	0.026	F	0.608	0
	Asian	4	2.541	0.873–7.397	0.087	R	0.000	88.4
	Adult	6	1.332	0.663–2.676	0.420	R	0.000	84.5

F = fixed effects model, R = random effects model.

2009), or data on other polymorphisms (Awasthi et al., 2011; de Faria et al., 2008). Thus, 10 reports met the inclusion criteria (Awasthi et al., 2011; Bijanzadeh et al., 2010; Blakey et al., 2009; Hirota et al., 2006; Howard et al., 2003; Jie et al., 2011; Lee et al., 2004; Qu et al., 2011; Su et al., 2008; Tripathi et al., 2011; Wang et al., 2006). One of these reports contained data on four different groups (Howard et al., 2003), and we analyzed these groups independently. Therefore, a total of 13 studies were included in this meta-analysis, which contained 4942 patients and 7933 controls, and eight Asian, three European, one African, and one Hispanic sample population. Eight studies were performed on adults, two studies on children, and three studies on a mixed group (Table 1). Distribution of ADAM33 genotype and allele frequency for asthmatic patients and controls in the population was provided in Supplementary Table 1. The distribution of ADAM33 polymorphisms in normal controls was not consistent with H–W equilibrium in two studies on V4 by Howard et al. Deviation from H–W equilibrium among controls implies potential bias during control selection or genotyping errors. We

excluded data not in-line with H–W expectations from the meta-analysis. Ethnicity-specific meta-analysis was conducted on Asian and on European populations. The number of studies used to examine ADAM33 polymorphisms was as follows: (1) S2 = nine, (2) ST+4 = eight, (3) F+1 = seven, (4) S1 = seven and (5) V4 = eight. Selected characteristics of these studies are summarized in Table 1.

3.2. Meta-analysis of the relationship between ADAM33 S2 and ST+4 polymorphisms and asthma

A summary of the association results between ADAM33 S2 and ST+4 polymorphisms and asthma is provided in Tables 2 and 3. Meta-analysis revealed no association between asthma and the ADAM33 S2 2 allele (OR = 1.522, 95% CI = 0.921–2.515, $p = 0.101$) (Table 2). Stratification by ethnicity indicated an association between the ADAM33 S2 2 allele and asthma in Europeans (OR = 0.912, 95% CI = 0.851–0.977, $p = 0.009$), but not in Asians (Table 2). Stratification

Table 3

Analysis of the association between the ADAM33 ST+4 polymorphism and asthma.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-Value	Model	p-Value	I ²
ST+4 2 vs. 1	Overall	8	0.783	0.762–0.999	0.048	R	0.089	43.3
	European	2	0.905	0.734–1.116	0.351	F	0.471	0
	Asian	4	0.854	0.689–1.060	0.153	R	0.058	59.8
	Adult	6	0.863	0.782–0.964	0.008	F	0.197	31.8
22 vs. 21 + 11 (recessive)	Overall	8	0.831	0.704–0.981	0.029	F	0.213	26.9
	European	2	0.864	0.609–1.205	0.412	F	0.201	38.8
	Asian	4	0.813	0.661–0.999	0.049	F	0.309	16.4
	Adult	6	0.853	0.713–1.021	0.084	F	0.193	36.4
22 + 21 vs. 11 (dominant)	Overall	8	0.838	0.723–0.971	0.018	F	0.254	22.0
	European	2	0.889	0.640–1.236	0.485	F	0.894	0
	Asian	4	0.844	0.618–1.153	0.287	R	0.075	56.5
	Adult	6	0.813	0.692–0.955	0.012	F	0.589	0
22 vs. 11 (codominant)	Overall	8	0.768	0.632–0.932	0.008	F	0.127	37.8
	European	2	0.868	0.568–1.328	0.515	F	0.492	0
	Asian	4	0.733	0.575–0.935	0.012	F	0.135	46.1
	Adult	6	0.774	0.626–0.957	0.018	F	0.175	34.8
22 vs. 21 (codominant)	Overall	8	0.880	0.737–1.049	0.154	F	0.418	1.51
	European	2	0.887	0.611–1.286	0.526	F	0.143	52.6
	Asian	4	0.863	0.692–1.076	0.191	F	0.589	0
	Adult	6	0.912	0.753–1.104	0.344	F	0.329	13.4

F = fixed effects model, R = random effects model.

by age indicated no association between the ADAM33 S2 2 allele and asthma in adults (OR = 1.429, 95% CI = 0.684–2.986, $p = 0.342$). Analysis using the recessive or additive model showed the same pattern for the ADAM33 S2 2 allele (Table 2, Fig. 1). We selected data for 22 vs. 11 for figures, because the homozygote comparison of a codominant model showed the meta-analysis result best (Fig. 1, 2). Meta-analysis revealed an association between asthma and the ADAM33 ST+4 2 allele (OR = 0.783, 95% CI = 0.762–0.999, $p = 0.048$) (Table 3). Analysis using the dominant, recessive, or additive model showed the same pattern for the ADAM33 ST+4 2 allele (Table 3, Fig. 2). Stratification by ethnicity indicated an association between the ADAM33 ST+4 polymorphism and asthma in Asians under the recessive and additive models (OR = 0.813, 95% CI = 0.661–0.999, $p = 0.049$; OR = 0.733, 95% CI = 0.575–0.935, $p = 0.012$) (Table 3). Furthermore, stratification by age indicated an association between the ADAM33 ST+4 2 allele and asthma in adults (OR = 0.863, 95% CI = 0.782–0.964, $p = 0.008$). Meta-analyses of the ADAM33 ST+4 polymorphism using the dominant or additive model showed the same pattern as meta-analysis of the ADAM33 ST+4 2 allele, that is, a significant association with asthma in adults (Table 3).

3.3. Meta-analysis of ADAM33 F+1, S1, and V4 polymorphisms and asthma

A summary of the association results between ADAM33 F+1, S1, and V4 polymorphisms and asthma is shown in Table 4. No association was found between asthma and ADAM33 F+1, S1, and V4 polymorphisms using the allele contrast, recessive, dominant, or additive models (OR for allele = 1.064, 95% CI = 0.844–1.342, $p = 0.598$; OR = 0.939, 95% CI = 0.729–1.209, $p = 0.626$; OR = 1.220, 95% CI = 0.815–1.825, $p = 0.334$) (Table 4). In addition, meta-analysis stratified by ethnicity and age revealed no association between asthma and ADAM33 F+1, S1, and V4 polymorphisms (Table 4).

3.4. Heterogeneity and publication bias

Between-study heterogeneity was found during analyses of ADAM33 polymorphisms except for the S1 polymorphism (Tables 2–4). In the analysis of S2 polymorphisms, heterogeneity was resolved in the meta-analysis of Europeans after stratification by ethnicity and was not found in adults under any genetic model. In the meta-analysis of ST+4 polymorphisms, heterogeneity was not found in Asians

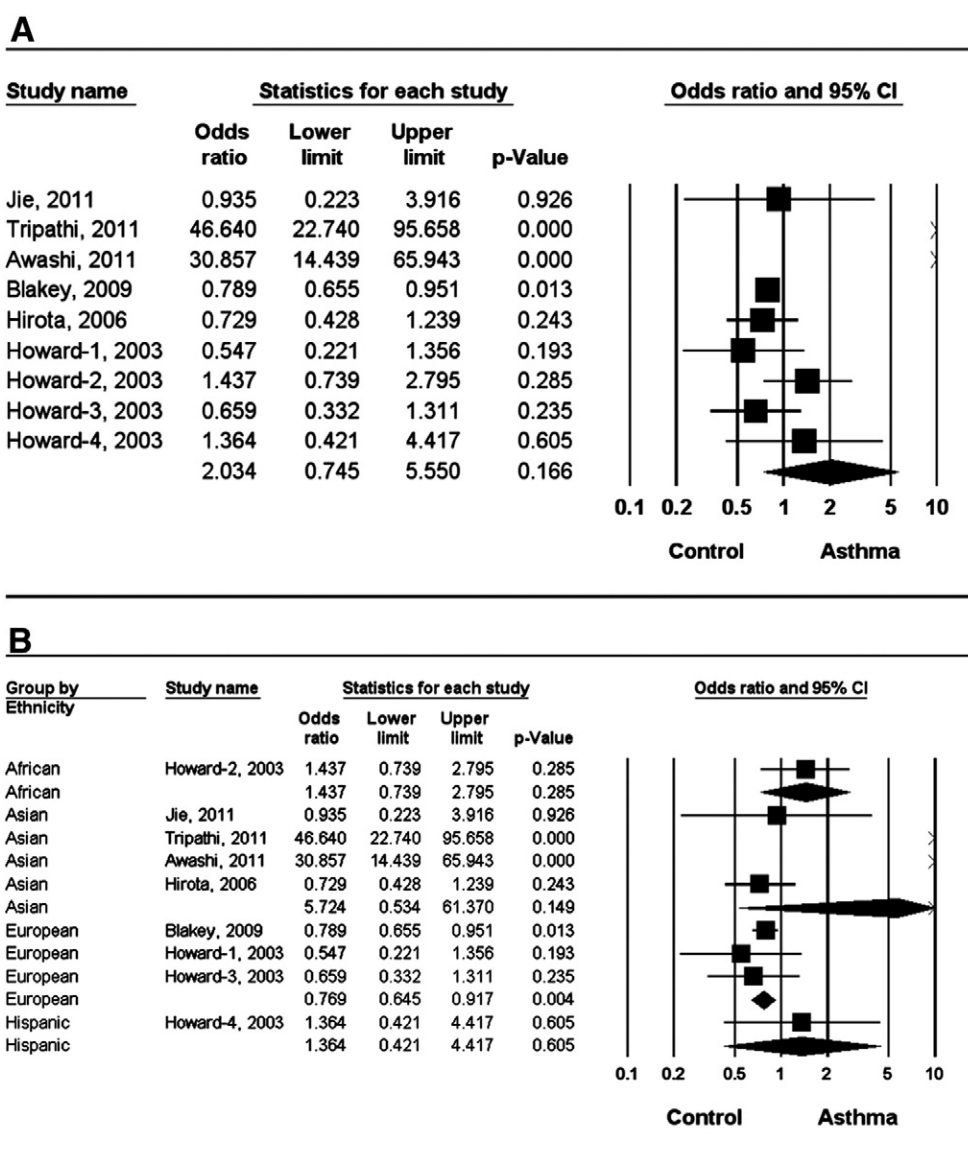
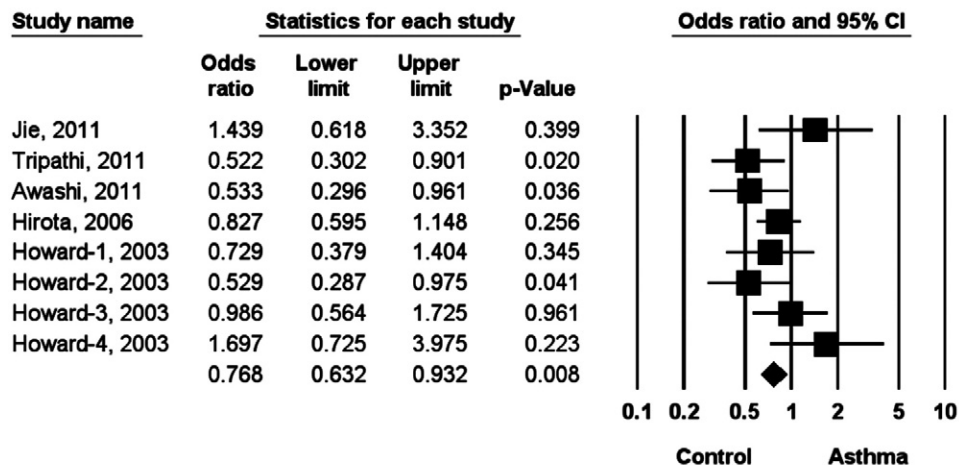


Fig. 1. ORs and 95% CIs of individual studies and pooled data for the 22 vs. 11 genotypes between asthma and the ADAM33 S2 polymorphism for all studies (A) and for each ethnic group (B).

A



B

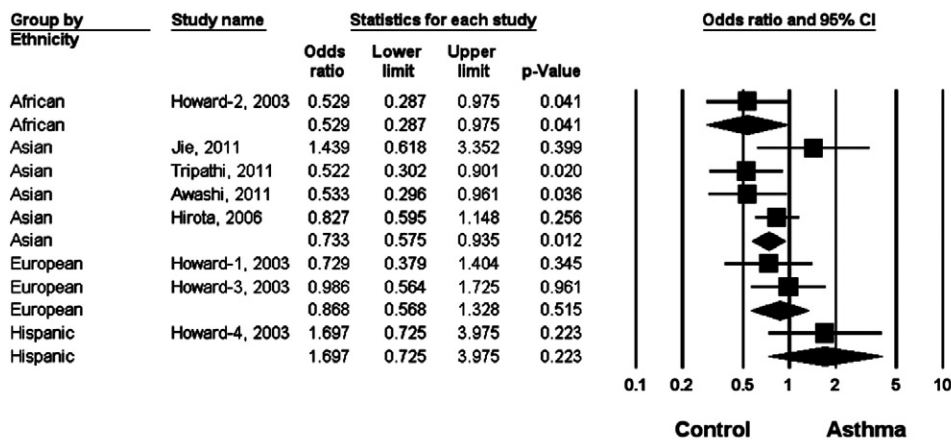


Fig. 2. ORs and 95% CIs of individual studies and pooled data for the 22 vs. 11 genotypes between asthma and the ADAM33 ST+4 polymorphism for all studies (A) and for each ethnic group (B).

under the recessive and additive models. The funnel plot, which is usually used to detect publication bias, was difficult to interpret because we included a relatively small number of studies. Egger's regression test showed no evidence of publication bias in the meta-analysis (Egger's regression test p -values > 0.1).

4. Discussion

Although asthma can have many causes, genetic factors are considered strong determinants. Therefore, researchers have focused on identifying specific genes involved in the disease (Arima and Fukuda, 2011;

Table 4

Analysis of the association between ADAM33 F+1, S1, and V4 polymorphisms and asthma.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-Value	Model	p-Value	I ²
F+1 2 vs. 1	Overall	7	1.064	0.844–1.342	0.598	R	0.000	89.4
	European	1	1.194	1.115–1.280	0.000	NA	NA	NA
	Asian	6	1.051	0.768–1.439	0.755	R	0.000	89.0
	Adult	3	0.779	0.540–1.124	0.181	R	0.000	87.3
S1 2 vs. 1	Overall	7	0.939	0.729–1.209	0.626	F	0.790	0
	European	2	0.879	0.612–1.265	0.488	F	0.434	0
	Asian	3	0.966	0.639–1.460	0.870	F	0.341	6.97
	Adult	5	0.881	0.672–1.156	0.361	F	0.868	0
V4 2 vs. 1	Overall	8	1.220	0.815–1.825	0.334	R	0.000	94.0
	European	NA	NA	NA	NA	NA	NA	NA
	Asian	6	1.264	0.773–2.067	0.351	R	0.000	95.3
	Adult	5	1.233	0.697–2.184	0.472	R	0.000	94.5

F = fixed effects model, R = random effects model.

Torgerson et al., 2011). Furthermore, airway structural changes due to airway remodeling play an important role in the development of airway obstruction in asthma. ADAM33 is expressed in lung fibroblasts and bronchial smooth muscle cells (Garlisi et al., 2003). Because of its expression profile, ADAM33 has been suggested to play a role in airway remodeling in patients with asthma and is considered a possible causative gene. In addition, it has been suggested that ADAM33 polymorphisms could lead to impaired or enhanced shedding of molecules associated with airway remodeling, and thus affect proliferation and inflammation in airways (Shapiro and Owen, 2002).

In the present study, we addressed associations between the ADAM33 S2, ST+4, F+1, S1, and V4 polymorphisms and asthma susceptibility. Meta-analysis stratified by ethnicity indicated an association between the ADAM33 S2 2 allele and asthma in Europeans (OR = 0.912, 95% CI = 0.851–0.977, $p = 0.009$), but not in Asians. Furthermore, we found an association between asthma and the ADAM33 ST+4 2 allele (OR = 0.783, 95% CI = 0.762–0.999, $p = 0.048$). Stratification by ethnicity indicated an association between the ADAM33 ST+2 polymorphism and asthma in Asians under the recessive and additive models (OR = 0.813, 95% CI = 0.661–0.999, $p = 0.049$; OR = 0.733, 95% CI = 0.575–0.935, $p = 0.012$). Stratification by age indicated an association between the ADAM33 ST+4 2 allele and asthma in adults (OR = 0.863, 95% CI = 0.782–0.964, $p = 0.008$). However, we found no association between asthma and ADAM33 F+1, S1, and V4 polymorphisms using the allele contrast, recessive, dominant, or additive models. Moreover, when data were stratified by ethnicity and age, meta-analysis revealed no association between asthma and ADAM33 F+1, S1, and V4 polymorphisms. The ADAM S2 polymorphism was observed to be associated with asthma in Europeans and the ADAM33 ST+4 polymorphism with Asians and adults. The reason why a particular polymorphism was associated with one population and the association was nil for another population may be due to the difference of the allele frequency of the ADAM33 polymorphisms among ethnic groups. For example, Europeans had a lower minor S2 allele prevalence than Asians. In terms of normal controls of this study, the frequencies of the S2 minor allele in the European and Asian populations were 17.0 and 32.2%, respectively.

The functional significance of the ADAM33 S2, ST+4, F+1, S1, and V4 polymorphisms remains unclear, and further functional studies are needed to clarify which ADAM33 polymorphisms alter gene expression and function. It has been suggested that some ADAM33 polymorphisms may affect alternative splicing, splicing efficiency, or mRNA turnover and accelerate the proliferation of smooth muscle cells and fibroblasts to cause bronchial hyperreactivity and subepithelial fibrosis (Van Eerdewegh et al., 2002). It is also possible that S2 and/or ST+4 are functional variants or in linkage disequilibrium with a causative polymorphism. In the present study, we identified an association between the ADAM33 S2 polymorphism and asthma in European patients and between the ADAM33 ST+4 polymorphism and asthma in Asians and adults. Our findings indicate age-related genetic susceptibility and ethnic differences in asthma pathogenesis. However, because of the limited number subjects, further studies are warranted to validate ethnic- and age-specific risk factors of asthma.

The present study had some limitations. First, heterogeneity and confounding factors may have distorted the analysis, and publication bias may have further affected the findings. Second, haplotype analysis may have provided more information and would have been more powerful than single polymorphism analysis. Haplotypes are considered to carry information about possible unobserved causal variants in the region (Noguchi et al., 2006), but an analysis of haplotypes was not possible because of inadequate haplotype data. Third, our ethnic-specific analysis only included data on Asian and European patients; thus, our results are applicable to only these ethnicities, and further studies are required in other ethnic populations. Fourth, data were not stratified by sex, disease severity, or clinical or environmental variables because of insufficient data.

In conclusion, this meta-analysis demonstrated that the ADAM33 S2 polymorphism confers susceptibility to asthma in Europeans and the ADAM33 ST+4 polymorphism is associated with asthma in Asians and adults, but no association was found between the ADAM33 F+1, S1, and V4 polymorphisms and asthma susceptibility. This meta-analysis provides further evidence that the ADAM33 gene plays a role in the etiology of asthma. Given what is known about the importance of ADAM33 in asthma, our findings suggest that ADAM33 S2 and ST+4 polymorphisms may modulate the development of asthma. Further studies are required to clarify the role of the ADAM33 gene in the pathogenesis of asthma.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.gene.2013.04.023>.

Conflict of interest statement

The authors have no financial and non-financial conflicts of interest to declare.

Acknowledgments

This study is supported by grant from Korea University Medical Center.

References

- Arima, M., Fukuda, T., 2011. Prostaglandin D and T(H)2 inflammation in the pathogenesis of bronchial asthma. *Korean J. Intern. Med.* 26, 8–18.
- Awasthi, S., Tripathi, P., Ganesh, S., Husain, N., 2011. Association of ADAM33 gene polymorphisms with asthma in Indian children. *J. Hum. Genet.* 56, 188–195.
- Bijanzadeh, M., et al., 2010. Association of IL-4 and ADAM33 gene polymorphisms with asthma in an Indian population. *Lung* 188, 415–422.
- Blakey, J.D., Sayers, I., Ring, S.M., Strachan, D.P., Hall, I.P., 2009. Positionally cloned asthma susceptibility gene polymorphisms and disease risk in the British 1958 Birth Cohort. *Thorax* 64, 381–387.
- Chae, S.C., Yoon, K.H., Chung, H.T., 2003. Identification of novel polymorphisms in the ADAM33 gene. *J. Hum. Genet.* 48, 278–281.
- de Faria, I.C., de Faria, E.J., Toro, A.A., Ribeiro, J.D., Bertuzzo, C.S., 2008. Association of TGF-beta1, CD14, IL-4, IL-4R and ADAM33 gene polymorphisms with asthma severity in children and adolescents. *J. Pediatr. (Rio J)* 84, 203–210.
- DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. *Control. Clin. Trials* 7, 177–188.
- Egger, M., Smith, G.D., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315, 629–634.
- Garlisi, C.G., et al., 2003. Human ADAM33: protein maturation and localization. *Biochem. Biophys. Res. Commun.* 301, 35–43.
- Higgins, J.P., Thompson, S.G., 2002. Quantifying heterogeneity in a meta-analysis. *Stat. Med.* 21, 1539–1558.
- Hirota, T., et al., 2006. Association between ADAM33 polymorphisms and adult asthma in the Japanese population. *Clin. Exp. Allergy* 36, 884–891.
- Howard, T.D., et al., 2003. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. *J. Allergy. Clin. Immunol.* 112, 717–722.
- Jie, Z., et al., 2009. The effects of Th2 cytokines on the expression of ADAM33 in allergen-induced chronic airway inflammation. *Respir. Physiol. Neurobiol.* 168, 289–294.
- Jie, Z., Hu, Z., Bai, C., Jin, M., 2011. ADAM33 gene polymorphisms associate with asthma susceptibility and severity in East China Han population. *J. Asthma* 48, 979–985.
- Kedda, M.A., Duffy, D.L., Bradley, B., O'Hehir, R.E., Thompson, P.J., 2006. ADAM33 haplotypes are associated with asthma in a large Australian population. *Eur. J. Hum. Genet.* 14, 1027–1036.
- Lee, J.H., et al., 2004. ADAM33 polymorphism: association with bronchial hyper-responsiveness in Korean asthmatics. *Clin. Exp. Allergy* 34, 860–865.
- Lee, Y.H., Harley, J.B., Nath, S.K., 2006a. Meta-analysis of TNF-alpha promoter – 308 A/G polymorphism and SLE susceptibility. *Eur. J. Hum. Genet.* 14, 364–371.
- Lee, Y.H., Rho, Y.H., Choi, S.J., Ji, J.D., Song, G.G., 2006b. Association of TNF-alpha – 308 G/A polymorphism with responsiveness to TNF-alpha-blockers in rheumatoid arthritis: a meta-analysis. *Rheumatol. Int.* 27, 157–161.
- Li, X., et al., 2010. Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions. *J. Allergy Clin. Immunol.* 125, 328–335 (e11).
- Lind, D.L., et al., 2003. Gonzalez Burchard E: ADAM33 is not associated with asthma in Puerto Rican or Mexican populations. *Am. J. Respir. Crit. Care Med.* 168, 1312–1316.
- Noguchi, E., et al., 2006. ADAM33 polymorphisms are associated with asthma susceptibility in a Japanese population. *Clin. Exp. Allergy* 36, 602–608.
- Qu, S., Sun, D., Wang, Y., Zhang, C., Lv, Y., Yao, L., 2011. Association of ADAM33 polymorphisms with childhood asthma in a northern Chinese population. *Exp. Mol. Pathol.* 91, 775–779.
- Raby, B.A., Silverman, E.K., Kwiatkowski, D.J., Lange, C., Lazarus, R., Weiss, S.T., 2004. ADAM33 polymorphisms and phenotype associations in childhood asthma. *J. Allergy Clin. Immunol.* 113, 1071–1078.

- Schedel, M., et al., 2006. The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. *Respir. Res.* 7, 91.
- Shapiro, S.D., Owen, C.A., 2002. ADAM-33 surfaces as an asthma gene. *N. Engl. J. Med.* 347, 936–938.
- Sharma, N., Tripathi, P., Awasthi, S., 2011. Role of Adam33 gene and associated single nucleotide polymorphisms in asthma. *Allergy & Rhinol* 2, 1–8.
- Su, D., Zhang, X., Sui, H., Lu, F., Jin, L., Zhang, J., 2008. Association of ADAM33 gene polymorphisms with adult allergic asthma and rhinitis in a Chinese Han population. *BMC Med Genet* 9, 82.
- Torgerson, D.G., et al., 2011. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat. Genet.* 43, 887–892.
- Tripathi, P., Awasthi, S., Prasad, R., Husain, N., Ganesh, S., 2011. Association of ADAM33 gene polymorphisms with adult-onset asthma and its severity in an Indian adult population. *J. Genet.* 90, 265–273.
- Undarmaa, S., et al., 2010. Replication of genetic association studies in asthma and related phenotypes. *J. Hum. Genet.* 55, 342–349.
- Van Eerdewegh, P., et al., 2002. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 418, 426–430.
- Vergara, C.I., et al., 2010. A six-SNP haplotype of ADAM33 is associated with asthma in a population of Cartagena, Colombia. *Int Arch Allergy Immunol* 152, 32–40.
- Wang, P., et al., 2006. Lack of association between ADAM33 gene and asthma in a Chinese population. *Int. J. Immunogenet* 33, 303–306.
- Werner, M., et al., 2004. Asthma is associated with single-nucleotide polymorphisms in ADAM33. *Clin Exp Allergy* 34, 26–31.
- Yoshinaka, T., et al., 2002. Identification and characterization of novel mouse and human ADAM33s with potential metalloprotease activity. *Gene* 282, 227–236.
- Zhang, X., Su, D., Sui, H., Jin, L., Lu, F., Zhang, J., 2009. Association of ADAM33 gene polymorphisms with adult concomitant allergic rhinitis and asthma in Chinese Han population. *Mol. Biol. Rep.* 36, 1505–1509.