Review Article

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Association of ADAM33 Gene Polymorphisms with Genetic Susceptibility to Asthma in Asian Populations: A Meta-Analysis

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Abstract

Method: The aim of present study was to assess the association of causative gene polymorphisms of ADAM33 in Asian population using Meta-analysis approach.We performed a literature search using the MEDLINE citation database and references in the identified reports. Data were analyzed using software Stata 11.2(Stata Corp, College Station, Texas, US). Thirteen studies and twelve ADAM33 gene polymorphisms were selected for meta-analysis, which included 3,270 patients and 2,922 controls. **Results:** On comparing data for "M" (Mutant allele) with the susceptibility to asthma as compared to the "L" (wild allele), four SNPs named as, S2, ST+5, T1 and Q-1 were observed to be associated with asthma. Likewise, on calculating "MM" (homozygous mutant genotype) *vs* "LL" (homozygous normal genotype), SNPs S2 and ST+5 showed association. After calculating, "LM" (heterozygous genotype) + "(MM *vs* LL)", SNP ST+5 was found to be associated and lastly when we compared "MM" vs "(LL+LM)", SNPs T1, S2 and ST+5 were found to be associated with asthma. **Conclusion:** To our knowledge, this is the first and most comprehensive genetic meta-analysis showing association of ADAM33 gene polymorphisms (Q-1, S2 and T1) with asthma in Asian population.

Keywords: Asian population; Meta-analysis; Single nucleotide polymorphisms; Association study; Case-control studies.

Introduction

Asthma is the most common chronic disease, effecting children and adults. It is predictable that around 300 million people in the world currently have asthma.[1] It is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.[2] Masoli *et al* published an article showing global burden of asthma, in which they have nicely represented prevalence of asthma in worldwide population on adults and children.[1]

While the exact role of ADAM33 in the pathogenesis of asthma is vague, studies have shown association of ADAM33 and its related SNPs with asthma. In the first report of ADAM33 as an asthma candidate gene in two Caucasian populations from the UK and the USA, Van Eerdewegh *et al*, identified a locus on the short arm of chromosome 20 and assessed 135 polymorphisms of 23 genes in this region and reported ADAM33 gene to be significantly associated with asthma.[3] A number of studies are available with very diverse results, suggesting ADAM33 SNPs role in asthma.[3-25] Recently Sharma *et al*, reviewed ADAM33 gene association with asthma on published literature[25], however results were not similar in all studied populations, some studies showed positive association of ADAM33 polymorphisms with asthma and another different set of studied populations were not associated with asthma.

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A candidate gene case–control approach, investigating polymorphisms, is generally taken to examine genetic risk factors for particular disease. Since asthma is a heterogeneous multifactorial disease, there is large number of candidate genes, which are involved in respiratory disorders like, COPD, allergic rhinitis, allergic dermatitis etc.[26-28] There is an improbability about the nature and number of genes involved in the development of asthma, due to lack of reproducibility of genetic case–control studies.[29] In the association studies, there are possibilities that some positive results might be specious and some negative findings might be a consequence of low statistical power. It could be due to their smaller sample size or methodological liabilities, such as the selection of an appropriate control group.[30] Meta-analysis might be a means of determining reflective results. Like, combining samples from several studies could make greater power than from individual studies or might increase trends for association in small individual studies. Meta-analysis might be useful to identify the causative gene polymorphisms with consistency and to quantify with accuracy the genetic risks. We conducted a complete meta-analysis of all ADAM33 gene polymorphisms in Asthma in Asian populations. Therefore the aim of present study was to assess the association of causative gene polymorphisms of ADAM33 in Asian population.

Materials and Methods

For study identification and selection of applicable studies, a literature search of the PubMed database was conducted to identify all articles that examined the association of the ADAM33 gene polymorphisms with asthma using clinically evident case-control study design. The terms "ADAM33", "ADAM33 gene and asthma", and "ADAM33 gene polymorphisms" were used as search criteria. The search results were limited to humans. All the studies that were published before March, 2012 were considered for primary screening. For meta-analysis inclusion and exclusion criteria were following:

Inclusion criteria

The articles written in English were only considered. To assess the aptness of the studies for inclusion in this meta-analysis, the publications were read in their entirety. Abstracts, editorials and review articles were excluded. All the case–control studies included in this meta-analysis had met the following criteria:

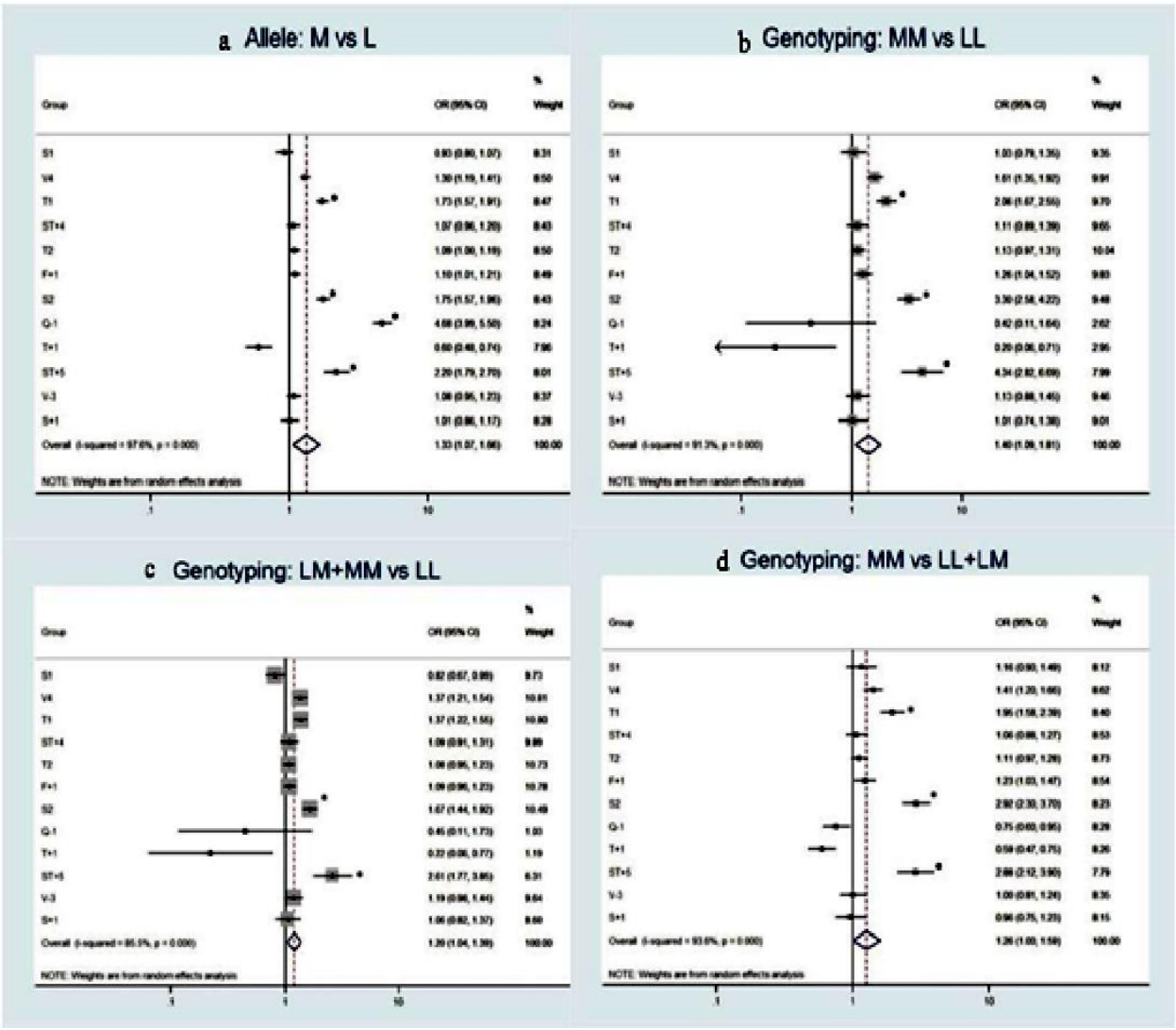
1) Asthma was diagnosed by physician/ pulmonologist who were experts in allergic diseases with characteristic symptoms, accompanied by preferred guidelines for asthma.
2) Studies contained original data (to ensure independence among studies), and
3) Studied that provided sufficient genotype data to calculate an odds ratio (OR).

Exclusion criteria

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),
5) Gender specific study and,
6) Control subjects were unrelated individuals without symptoms and family history of asthma, selected randomly from the same geographic region.

Figure 1: Schematic representation of the ADAM33 gene on chromosome 20. (A) Chromosome 20 showing ADAM33 gene position 20p13. (B) Region covered by polymorphisms done on Asian population and covered size in Kb. (C) Exons and size in base pairs (D) domain structure (E) Functions of ADAM33 domain



Data extraction

The following informations were extracted from each study: name of the first author, year of publication, country, journal, racial descent of study population, demographics, number of cases and controls, genotyping methods, genotype and allele distributions and confirmation of diagnosis. If allele frequencies were not given, they were calculated from the corresponding genotype distributions.

Statistical analysis

Data were analyzed using software Stata 11.2(Stata Corp, College Station, Texas, US). For each polymorphisms of ADAM33 gene, meta-analysis was performed to examine the overall association for the allele contrast, the contrast of homozygotes, and the recessive, dominant and additive models. To measure the strength of genetic association for each gene variant, the odds ratios (ORs), together with the 95% confidence interval (CI) and the corresponding P value (the P value being significant if <0.05) were calculated. Heterogeneity between the studies was examined by Q-statistic, which is a weighted sum of squares of the deviations of individual

study OR estimates from the overall estimate.[31,32] The heterogeneity was considered statistically significant with P<0.10. Quantification of the heterogeneity was done with the I^2 metric (I^2 = (Q - df)/Q), which is independent of the number of studies in the meta-analysis.[33] This explains the variance of effect estimate attributable to heterogeneity and its values falls between 0–100%, with higher values denoting greater degree of heterogeneity (I2 = 0–25%, no heterogeneity; I2 = 25–50%, moderate heterogeneity; I2 = 50–75%, large heterogeneity; I2 = 75–100%, extreme heterogeneity).[31,32] The random-effects pooled ORs were calculated by the DerSimonian and Liard method.[34] As the studies are both clinically and methodologically diverse, heterogeneity between studies is an expected outcome.[35] If heterogeneity existed between studies, a pooled OR was estimated by the random-effects model, because this model assumes a genuine diversity in the results of the studies, incorporating the calculations of inter-study variability and provides wider CIs.[32] In this article, the results from the random-effects model are reported only. To assess the publication bias for allele contrasts, the Egger regression test for funnel plot asymmetry[31,32,36] and the begs- Mazumdar test, which is based on Kendall's tau[37], were carried out.

Results

Study inclusion

The initial search with the key words and subject terms identified a total of 19 studies. Of these, based on the penetrating criteria, fourteen articles were taken.[4-9,11-16,38,39] Due to unavailability of the genotype data, one study was excluded.[12] Finally, thirteen studies[4-9,11,13-16,38,39] were considered for the meta-analysis on twelve ADAM 33 gene polymorphisms namely, S1, V4, T1, ST+4, T2, F+1, S2, Q-1, T+1, ST+5, V-3, and S+1. **Figure 1** represents schematic representation of the ADAM33 gene on chromosome 20, gene position on chromosome 20p13, region covered by polymorphisms done on Asian population and covered size in Kb and gives an overview of gene exons and size in base pairs, domain structure and their functions.

We only included Asian populations for meta-analysis. All studies taken were in Hardy– Weinberg equilibrium (HWE). Genotype determination in the included studies was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR–RFLP) method in seven studies[4-5,11,13,15,16,38,39] and in other studies it was done by allele specific polymerase chain reaction with fluorescence melting curve[6], using single based extension and electrophoresis[9], using direct sequencing [14] and using Taqman and PCR-RFLP methods.[7] In our personal communication genotyping (SNPs, Q-1, T1, T2, and S1) was done using PCR-RFLP method. We gave common name to studied SNPs' genotypes and allele as; mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

Summary statistics

Characteristics of the included studies on ADAM33 gene polymorphisms are shown in **Table 1**. The genotype distributions and the allele frequencies on all included Asian populations' sample size are mentioned in **Table 2**. Study specific genotypic and allelic data are provided in **supplementary file 1**.

Main results

Thirteen studies and twelve ADAM33 gene polymorphisms were selected for meta-analysis, which included 3,270 patients and 2,922 controls. After combining all data for meta-analysis of ADAM33 gene polymorphisms named as S1, V4, T1, ST+4, T2, F+1, S2, Q-1, T+1, ST+5, V-3, and S+1, four of the twelve SNPs were significantly associated with asthma in meat-analysis (**Figure 2**) with a maximum odds ratio (OR)

Table 1: characteristic of the studies of ADAM33 gene polymorphisms and asthma on Asian population

S. no.	Population	Cases	Control	Polymorphisms	References
1	Northern Chinese	412 (48.30% female); mean age 7.74 ± 2.78 years	397 (48.36% female); mean age 7.52 ± 2.95 years	F+1, T+1, T2, T1, V4 and Q-1	Qu *et al*, 2011[11]
2	East Chinese Han	150 (54.0% female); age range 13-75 in years	74 (56.8% female); age range 20-69 in years	F+1, ST+4, S1, S2, T1 and T2	Jie *et al*, 2011[8]
3	Chinese	329(43.16% female); age in years, median(range); 39.88 (13-69)	316 (47.78% female); age in years, median(range); 43.0(22-69)	F+1, S2, T2 and V4	Chi *et al*, 2011[6]
4	Indian	175 (30.9% female); mean age 33.7 ± 11.3years	235 (20.6% female); mean age 31.9 ± 9.2	F+1,V4, ST+4, ST+5 and S2	Tripathi *et al*, 2011[15]
5	Indian	211 (32.2%female); mean age 74.39 ± 45.76 months	137 (29.9% female); mean age 73.61 ± 42.56 months	F+1,V4, ST+4, ST+5 and S2	Awasthi *et al*, 2011[4]
6	South Indian	100 (45% female); age range: 6 months to 80 years	50 (12% female); age range: 6 months to 80 years	T1	Bijanzadeh *et al*, 2010[5]
7	Chinese Han	181 (37.02%female); mean age 36.69 ± 11.53 years	151 (35.76% female); mean age 37.18 ± 10.60 years	V4, T+1, T2, T1, S1 and Q-1	Su *et al*, 2008[13]
8	Thai	200 (42% female); mean age 29.86 years	100 (54% female); mean age 26 years	ST+4, S2 and V4	Thongngarm *et al*, 200814
9	Japanese	504 (male: female ratio = 1.0 : 1.29); mean age 48.7,16–91 years	651 (male : female ratio = 2.56 : 1.0); mean age 44, 18–83 years	F+1, S2, ST+4, T1, T2, V-3 and V4	Hirota *et al*, 2006
10	Korean	326 (59.82%female); median (range); 48(11-78) in years	151 (47.02% female) median (range); 27(10-74) in years	S1, T1 and V4	Lee *et al*, 2004[9]
11	Chinese	296 (48.31%female); average age 43.32 years	270; (46.67%female) average age 41.91 years	F+1, T1, S+1	Wang *et al*, 2000[16]
12	Indian	386 (68.4%female) mean age 18.7 ± 15.9 years	390 (76.2% female) mean age 22.87 ± 14.54 years	V-3, S+1 and T+1	Tripathi *et al*, 2012[38]
13	Indian	386 (68.4%female) mean age 18.7 ± 15.9 years	390 (76.2% female) mean age 22.87 ± 14.54 years	Q-1, T1, T2 and S1	Awasthi et al, 2012 [39]

Table 2: The distribution of the A disintegrin and metalloprotease 33 (ADAM33) genotypes and the allelic frequency for asthmatic patients and controls (values in parentheses are the corresponding percentages) on Asian populations

SNPs	Populations	Distribution of ADAM33 SNP's genotypes						Frequency of ADAM33 SNPs alleles			
		LL, n (%)		LM, n (%)		MM, n (%)		L, n (%)		M, n (%)	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
S1	East Chinese Han, Chinese Han, Korean, Indian	613 (59.63)	418 (54.64)	236 (22.96)	229 (29.93)	179 (17.41)	118 (15.42)	1462 (71.11)	1065 (69.61)	594 (28.89)	465 (30.39)
V4	Northern Chinese, Chinese, Indian, Thai, Japanese, Korean	896 (36.23)	873 (43.72)	1107 (44.76)	840 (42.06)	470 (19.01)	284 (14.22)	2899 (58.61)	2584 (64.75)	2047 (41.39)	1408 (35.25)
T1	Northern Chinese, East Chinese Han, South Indian, Chinese Han, Japanese, Korean, Chinese, Indian	1078 (46.61)	1393 (65.55)	826 (35.71)	584 (27.48)	409 (17.68)	148 (6.96)	2982 (64.46)	3370 (79.29)	1644 (35.54)	880 (20.71)
ST+4	Indian, Thai, Japanese,	313 (25.47)	330 (27.16)	593 (48.25)	579 (47.65)	323 (26.28)	306 (25.19)	1219 (49.59)	1239 (50.99)	1239 (50.14)	1191 (49.01)
T2	Northern Chinese, East Chinese Han, Chinese, Chinese Han, Japanese, Indian	822 (42.33)	863 (44.26)	501 (25.80)	510 (26.15)	619 (31.87)	577 (29.59)	2145 (55.23)	2236 (57.33)	1739 (44.77)	1664 (42.67)
F+1	Northern Chinese, East Chinese Han, Chinese, Indian, Chinese, Japanese	858 (41.43)	912 (43.55)	908 (43.84)	924 (44.13)	305 (14.73)	258 (12.32)	2624 (63.35)	2748 (65.62)	1518 (36.65)	1440 (34.38)
S2	East Chinese Han, Chinese, Indian, Thai, Japanese,	695 (44.93)	878 (57.61)	575 (37.17)	540 (35.43)	277 (17.91)	106 (6.96)	1965 (63.51)	2296 (75.33)	1129 (36.49)	752 (24.67)
Q-1	Northern Chinese, Chinese Han, Thai, Japanese,	7 (0.72)	3 (0.32)	204 (20.84)	158 (16.84)	768 (78.45)	777 (82.84)	218 (11.13)	164 (8.74)	1740 (88.87)	1712 (91.26)
T+1	Northern Chinese, Chinese Han, Indian	14 (1.43)	3 (0.32)	214 (21.86)	140 (14.93)	751 (76.71)	795 (84.75)	242 (12.36)	146 (7.78)	1716 (87.64)	1730 (62.22)
ST+5	Indian	44 (11.40)	98 (25.13)	155 (40.16)	196 (50.26)	187 (48.45)	96 (24.62)	243 (31.48)	392 (50.26)	529 (68.52)	388 (49.74)
V-3	Japanese, Indian	216 (25.68)	340 (33.17)	425 (50.54)	454 (44.29)	200 (23.78)	231 (22.54)	857 (50.95)	1134 (55.32)	825 (49.05)	916 (44.68)
S+1	Chinese, Indian	157 (23.02)	159 (24.09)	361 (52.93)	337 (51.06)	164 (24.05)	164 (24.85)	675 (49.49)	655 (49.62)	689 (5051)	665 (50.38)

Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

Figure 2: Forest plots on studied SNPs
a)M vs L; b) MM vs LL; c) LM+MM vs LL and d) MM vs LL+LM ; where Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM.

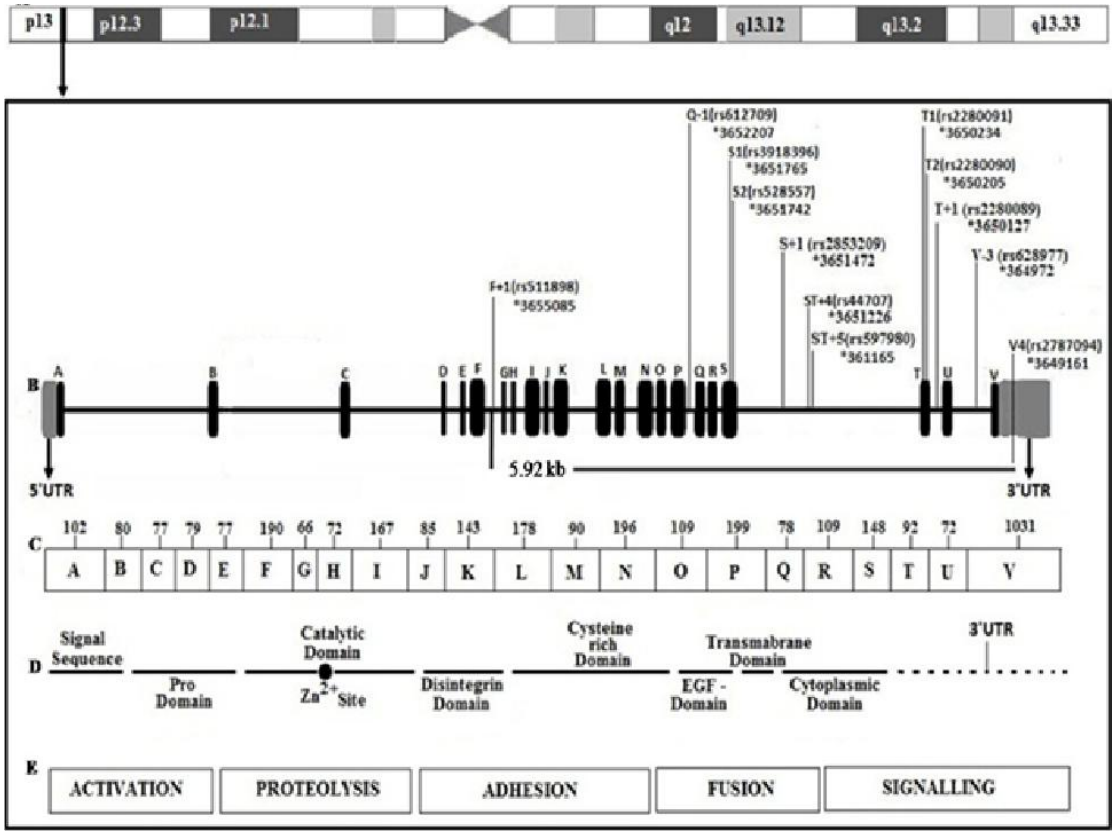


Table 3: Association of Taken ADAM33 gene polymorphisms for meta-analysis in different populations

S. no.	Population	C^1/C^2	Polymorphisms												
1			S1	V4	T1	ST+4	T2	F+1	S2	Q-1	T+1	ST+5	S+1	V-3	References
	Northern Chinese	412/397	NA	AR	AR	ND	NA	NA	ND	NA	AR	ND	ND	ND	Qu *et al*, 2011[11]
2	East Chinese Han	150/74	NA	ND	AR	NA	AR	AR	NA	ND	ND	ND	ND	ND	Jie *et al*, 2011[8]
3	Chinese	329/316	ND	NA	ND	ND	NA	NA	AR	ND	ND	ND	ND	ND	Chi *et al*, 2011[6]
4	Indian	175/235	NA	AR	NA	AR	NA	AR	AR	NA	NA	AR	ND	ND	Tripathi *et al*, 2011[15]
5	Indian	211/137	ND	AR	ND	AR	ND	AR	AR	ND	ND	AR	ND	ND	Awasthi *et al*, 2011[4]
6	South Indian	100/50	ND	ND	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	Bijanzadeh *et al*, 2010[5]
7	Chinese Han	181/151	NA	AR	AR	ND	AR	ND	ND	AR	NA	ND	ND	ND	Su *et al*, 2008[13]
8	Thai (DNG)	200/100	ND	NA	ND	AR	ND	ND	AR	ND	ND	ND	ND	ND	Thongngarm *et al*, 200814
9	Japanese	504/651	ND	NA	AR	NA	AR	NA	AR	ND	ND	ND	ND	NA	Hirota *et al*, 2006
10	Korean	326/151	NA	NA	NA	ND	ND	ND	ND	ND	ND	ND	ND	ND	Lee *et al*, 2004[9]
11	Chinese	296/270	ND	ND	NA	ND	ND	NA	ND	ND	ND	ND	NA	ND	Wang *et al*, 2000[16]
12	Indian	386/390	ND	ND	ND	ND	ND	ND	ND	ND	NA	ND	NA	NA	Tripathi *et al*, 2012[38]
13	Indian	386/390	AR	ND	AR	ND	AR	ND	ND	NA	ND	ND	ND	ND	Awasthi et al, 2012 [39]

1=case; 2=control; NA=not associated; AR=associated with risk of disease asthma; ND=not done; DNG= Details not given

of 4.68 [95% confidence interval (CI) (3.99,5.50)] for Q-1 when we compared M allele with the susceptibility to asthma as compared to the L allele under the random effects model. SNPs S2, ST+5 and T1 were also found to be associated with risk of asthma. [(OR=1.75, 95 % CI=1.57-1.96); (OR=2.20, 95 %CI=1.79-2.70) and (OR=1.73, 95%CI= (1.57-1.91)]

Genotype combinations "MM" vs. "LL", "(LM+MM)" vs "LL" and "MM" vs "(LL+LM)" were made for analysis to find association in all aspects. On calculating MM

Table 1: Distribution of genotype and allele frequency of ADAM33 polymorphisms in asthmatic patients and controls

	Trial name	Publication year	Case LL	Case LM	Case MM	Case L allele	Case M allele	Control LL	Control LM	Control MM	Control L allele	Control M allele
id	name											
V4	Tripathi *et al*,	2011	17 (9.71)	70 (40.0)	88 (40.3)	104 (29.7)	246 (29.7)	47 (18.6)	133 (52.5)	73 (28.9)	227 (44.9)	279 (55.1)
V4	Qu *et al*,	2011	141 (34.2)	198 (48.1)	73 (17.7)	480 (58.3)	344 (41.8)	232 (58.4)	134 (33.8)	31 (7.8)	598 (75.3)	196 (24.)
V4	Chi *et al*,	2011	151 (45.9)	133 (40.4)	45 (13.7)	435 (66.1)	223 (33.9)	148 (46.8)	132 (41.8)	36 (11.4)	428 (67.7)	204 (32.3)
V4	Awasthi *et al*,	2010	34 (16.1)	90 (42.7)	87 (41.2)	158 (37.4)	264 (62.6)	33 (24.1)	58 (42.4)	46 (33.6)	124 (45.3)	150 (54.7)
V4	Thongngarm *et al*,	2008	87 (43.5)	94 (47.0)	19 (9.5)	268 (67.0)	132 (33.0)	40 (40.0)	47 (47.0)	13 (13.0)	127 (63.5)	73 (36.5)
V4	Su *et al*,	2008	49 (27.1)	78 (43.1)	54 (29.8)	176 (48.6)	186 (51.4)	113 (74.8)	32 (21.2)	6 (4.0)	258 (85.4)	44 (14.6)
V4	Hirota *et al*,	2006	292 (44.6)	298 (45.5)	65 (9.9)	882 (67.3)	428 (32.7)	198 (40.0)	233 (47.1)	64 (12.9)	629 (63.5)	361 (36.5)
V4	Lee *et al*,	2004	125 (40.3)	146 (47.1)	39 (12.6)	396 (63.9)	224 (36.1)	61 (41.5)	71 (48.3)	15 (10.2)	193 (65.7)	101 (34.4)
S1	Jie *et al*,	2011	130 (86.7)	20 (13.3)	0 (0.0)	280 (93.3)	20 (6.7)	68 (91.9)	6 (8.1)	0 (0.0)	142 (95.5)	8 (4.1)
S1	*Awasthi *et al*,	2012	44 (11.4)	163 (42.2)	179 (46.4)	251 (32.5)	521 (67.5)	95 (24.4)	177 (45.4)	118 (30.3)	367 (47.1)	413 (53.0)
S1	Su *et al*,	2008	140 (77.4)	41 (22.7)	0 (0.0)	321 (88.7)	41 (11.3)	110 (72.9)	41 (27.2)	0 (0.0)	261 (86.4)	41 (13.6)
S1	Lee *et al*,	2003	299 (96.1)	12 (3.9)	0 (0.0)	610 (98.1)	12 (1.9)	145 (96.7)	5 (3.3)	0 (0.0)	295 (98.3)	5 (1.7)
T1	*Awasthi *et al*,	2012	58 (15.3)	170 (44.0)	158 (40.9)	286 (37.1)	486 (63.0)	100 (25.5)	183 (46.9)	107 (27.4)	383 (49.1)	397 (50.9)
T1	Qu *et al*,	2011	140 (34)	185 (44.9)	87 (21.1)	465 (56.7)	359 (43.6)	240 (60.5)	129 (32.5)	28 (7.1)	609 (76.7)	185 (23.3)
T1	Jie *et al*,	2011	118 (78.7)	32 (21.3)	0 (0.0)	268 (89.3)	32 (10.7)	69 (93.2)	5(6.8)	0 (0.0)	143 (96.6)	5 (3.4)
T1	Bijanzadeh *et al*,	2010	50 (62.5)	29 (36.3)	1 (1.3)	129 (80.6	31 (19.4)	35 (70.0)	15 (30.0)	0 (0.0)	85 (85.0)	15 (15.0)
T1	Su *et al*,	2008	63 (34.8)	78 (43.1)	40 (22.1)	204 (56.4)	158 (43.7)	117 (77.5)	29 (19.2)	5 (3.3)	263 (87.1)	39 (12.9)
T1	Hirota *et al*,	2006	134 (27.2)	239 (48.5)	120 (24.3)	507 (51.4)	180 (48.6)	471 (73.0)	68 (26.1)	6 (0.9)	1110 (86.1)	180 (14.0)
T1	Lee *et al*,	2004	265 (84.1)	48 (15.2)	2 (0.6)	578 (91.8)	52 (8.3)	125 (84.5)	22 (14.9)	1 (0.7)	272 (91.9)	24 (8.1)
ST +4	Jie *et al*,	2011	47 (31.3)	79 (52.7)	24 (16.0)	173 (57.7)	127 (42.3)	31 (43.0)	32 (42.0)	11 (15.0)	128 (64.0)	72 (36.0)
ST +4	Tripathi *et al*,	2011	31 (17.7)	78 (44.6)	66 (37.7)	140 (40.0)	210 (60.0)	63 (24.9)	120 (47.4)	70 (27.7)	246 (48.6)	260 (51.4)
ST +4	Awasthi *et al*,	2011	38 (18)	94 (44.6)	79 (37.4)	170 (40.3)	252 (59.7)	37 (27.0)	59 (43.1)	41 (29.9)	133 (48.5)	141 (51.5)
ST +4	Thongngarm *et al*,	2008	63 (31.5)	103 (51.5)	34 (17.0)	229 (57.3)	171 (45.8)	43 (43.0)	42 (42.0)	15 (15.0)	128 (64.0)	72 (36.0)
ST +4	Hirota *et al*,	2004	134 (27.2)	239 (48.5)	120 (24.3)	507 (51.4)	479 (48.6)	156 (24.0)	326 (50.1)	169 (26.0)	638 (49.0)	664 (51.0)
T2	*Awasthi *et al*,	2012	54 (14)	168 (43.5)	164 (42.5)	276 (35.8)	496 (64.3)	101 (25.9)	192 (49.2)	97 (24.9)	394 (50.5)	386 (49.5)
T2	Chi *et al*,	2011	248 (75.4)	79 (24.0)	2 (0.6)	575 (87.4)	83 (12.6)	246 (77.9)	67 (21.2)	3 (1.0)	559 (88.5)	73 (11.6)
T2	Qu *et al*,	2011	7 (1.7)	86 (20.9)	319 (77.4)	100 (12.1)	724 (87.9)	2 (0.5)	69 (17.4)	326 (82.1)	73 (9.2)	721 (90.8)
T2	Jie *et al*,	2011	127 (84.7)	22 (14.7)	1 (0.7)	276 (92.0)	24 (8.0)	72 (97.3)	2 (2.7)	0 (0.0)	146 (98.7)	2 (1.4)
T2	Su *et al*,	2008	4 (2.21)	49 (27.1)	128 (70.7)	57 (15.8)	305 (84.3)	0 (0.0)	12 (8.0)	139 (92.1)	12 (4.0)	290 (96.0)
T2	Hirota *et al*,	2006	382 (78.9)	97 (20.0)	5 (1.0)	861 (89.0)	107 (11.1)	442 (71.0)	168 (27.0)	12 (1.9)	1052 (84.6)	192 (15.4)
F+1	Awasthi	2011	39 (18.5)	94 (44.6)	78 (37.0)	172 (40.8)	250 (59.2)	40 (29.2)	73 (53.3)	24 (17.5)	153 (55.8)	121 (44.2)
F+1	Tripathi	2011	25 (14.3)	77 (44.0)	73 (41.7)	127 (36.3)	223 (63.7)	61 (24.1)	116 (45.9)	76 (30.0)	238 (47.0)	268 (53.0)

	Trial name	Publication year	Case LL	Case LM	Case MM	Case L allele	Case M allele	Control LL	Control LM	Control MM	Control L allele	Control M allele
id	name											
F+1	Qu *et al*,	2011	178 (43.2)	19 (48.1)	36 (8.7)	554 (67.2)	270 (32.8)	173 (43.6)	182 (45.8)	42 (10.6)	528 (66.5)	266 (33.5)
F+1	Jie *et al*,	2011	72 (48)	67 (44.7)	11 (7.3)	211 (70.3)	89 (29.7)	52 (70.3)	18 (24.3)	4 (5.4)	122 (82.7)	26 (17.6)
F+1	Chi *et al*,	2011	177 (53.8)	125 (38.0)	27 (8.2)	479 (72.8)	179 (27.2)	183 (57.9)	118 (37.3)	15 (4.8)	484 (76.6)	148 (23.4)
F+1	Hirota *et al*,	2006	214 (43)	224 (45.0)	60 (12.1)	652 (65.5)	344 (34.5)	272 (42.0)	291 (45.0)	84 (13.0)	835 (64.5)	459 (35.5)
Q-1	*Awasthi *et al*,	2012	0 (0)	60 (15.5)	326 (84.5)	60 (7.8)	712 (92.2)	0 (0.0)	60 (15.4)	330 (84.6)	60 (7.7)	720 (92.3)
Q-1	Qu *et al*,	2011	7 (1.7)	100 (24.3)	305 (74.0)	114 (13.8)	710 (86.2)	3 (0.8)	87 (21.9)	307 (77.3)	933 (14.7	701 (88.3)
Q-1	Su *et al*,	2008	0 (0)	44 (24.3)	137 (75.7)	44 (12.2)	318 (87.9)	0 (0.0)	11 (7.3)	140 (92.7)	11 (3.6)	291 (96.4)
T+1	Awasthi *et al*,	2012	0 (0)	80 (20.7)	306 (79.3)	80 (10.4)	692 (89.6)	0 (0.0)	60 (15.4)	330 (84.6)	60 (7.7)	720 (92.3)
T+1	Qu *et al*,	2011	14 (3.4)	97 (23.5)	301 (73.1)	125 (15.2)	699 (84.8)	3 (0.8)	39 (9.8)	355 (80.4)	45 (5.7)	749 (94.3)
T+1	Su *et al*,	2008	0 (0)	37 (20.4)	144 (79.6)	37 (10.2)	325 (89.8)	0 (0.0)	41 (27.2)	110 (72.9)	41 (13.6)	261 (86.4)
ST+5	Awasthi *et al*,	2011	26 (12.3)	94 (44.6)	91 (43.1)	146 (34.6)	276 (65.4)	33 (24.1)	67 (48.9)	37 (27)	133 (48.5)	141 (51)
ST+5	Tripathi *et al*,	2011	18 (10.3)	61 (34.9)	96 (54.9)	97 (27.71)	253 (72.3)	65 (25.7)	129 (51)	59 (23.3)	259 (51.2)	247 (49)
V-3	Awasthi *et al*,	2012	76 (19.7)	180 (46.6)	130 (33.7)	332 (43.0)	440 (57.0)	67 (17.2)	175 (44.9)	148 (38.0)	309 (39.6)	471 (60.4)
V-3	Hirota *et al*,	2006	185 (37)	245 (49.0)	70 (14.0)	615 (61.5)	385 (38.5)	273 (43.0)	279 (43.9)	83 (13.1)	825 (65.0)	445 (35.0)
S2	Jie *et al*,	2011	92 (61.3)	52 (34.7)	6 (4)	236 (78.7)	64 (54.3)	43 (58.1)	28 (37.8)	3 (4.1)	114 (77.0)	34 (22.9)
S2	Awasthi *et al*,	2011	18 (8.5)	85 (40.3)	108 (51.2)	121 (28.7)	301 (71.3)	72 (52.6)	51 (37.2)	14 (10.2)	195 (71.2)	79 (28.8)
S2	Tripathi *et al*,	2011	20 (11.4)	67 (38.3)	88 (50.3)	107 (30.6)	243 (69.4)	159 (62.9)	79 (31.2)	15 (5.9)	397 (78.5)	109 (21.5)
S2	Chi *et al*,	2011	152 (46.2)	135 (41.0)	42 (12.8)	439 (66.7)	219 (33.3)	178 (56.3)	110 (34.8)	28 (8.9)	466 (73.7)	166 (26.3)
S2	Thongngarm *et al*,	2008	114 (57)	77 (38.5)	9 (4.5)	305 (76.3)	95 (23.8)	72 (72.0)	21 (21.0)	7 (7.0)	165 (82.5)	35 (17.5)
S2	Hirota *et al*,	2006	299 (62.0)	159 (32.9)	24 (4.9)	757 (78.5)	207 (21.5)	354 (54.9)	251 (38.9)	39 (6.1)	959 (74.5)	329 (25.5)

Mutant allele= M, wild type allele= L, homozygous normal genotype= LL, heterozygous genotype=LM, homozygous mutant genotype=MM; *= personal communication;

vs LL association of SNPs S2 and ST+5 were observed with maximum OR of 3.30 [95% CI (2.58, 4.22)] and 4.34 [95% CI (2.82, 6.69)], respectively. After calculating (LM+MM) *vs* LL, none of the SNPs showed maximum OR with disease asthma, except ST+5 with the OR of 2.61 [95% CI (1.77, 3.85)]. However meta-analysis for this SNP was done only on 2 studies. And lastly when we analyzed combination of genotype MM *vs* (LL+LM) three of eleven SNPs namely, T1, S2 and ST+5 were found as risk with [OR= 1.95; 95% CI (1.58, 2.39)], 2.92 [95% CI (2.30, 3.70)] and 2.88 [95% CI (2.12, 3.90)], respectively.

Publication bias

We applied Begg-Mazumdar test, Kendall's tau and Egger's test to analyze publication Bias. All the tests showed no significant publication bias, P>0.05.

Discussion

This is the first report evaluating the role of ADAM33 gene polymorphisms in the predisposition of asthma in Asian population and we observed association of SNPs Q-1, S2, ST+5 and T1 with asthma, however we found only two studies showing association of ST+5 with susceptibility to asthma and both was from India[4,15], therefore more studies are needed from Asian countries to get clear picture of association of SNP ST+5 with

asthma in Asian population. Previously Blakey *et al[24]* conducted meta-analysis on Caucasian populations of all existing data demonstrated either positive or negative association results with asthma, study included total 13 SNPs named as, F+1, M+1, Q-1, S1, S2, ST+4, ST+5, ST+7, T1, T2, T+1, V-1 and V4 and found SNPs F+1 and ST+7 to be statistically significantly associated with asthma with a maximum OR of 1.46 (95% CI 1.21 to 1.76) for ST+7 (p=0.0001). However, study was done on Caucasian populations only. ST+7 SNP had not been included in our study as we did not find much study on Asian population for performing the analysis.

Our study, in the context of the Asian populations, presented an overview of the studies of the ADAM33 gene polymorphisms that have been examined for their association with asthma.

Summary of association of studied polymorphisms in their studies are mentioned in Table 3. A study conducted on Chinese population by Wang *et al* did not find any association of SNPs, namely S+1, T1 and F+1, with asthma. [16] In another study by Su *et al* on Chinese Han population analyzing six SNPs of ADAM33 gene, namely V4, T+1, T2, T1, S1 and Q-1, for association with asthma, found that V4, T2, T1 and Q-1, increase risk of susceptibility.[13]

Thongngarm *et al* in their study on Thai population found a positive association between ADAM33 polymorphisms S2 and ST+4 with asthma susceptibility.[14] Bijanzadeh *et al* failed to find an association between asthma and the T1 SNP of ADAM33 gene in a southern Indian population.[5] However, another case control study, conducted in Northern India to assess association of ADAM33 gene polymorphisms namely, F+1, S2, ST+4, ST+5 and V4, with asthma in children and in adults , showed significant association of all of them with the disease.[4,15] Chi *et al* conducted study on Chinese population found association of S2 with asthma, while SNPs F+1, T2 and V4 were not associated with risk of disease asthma.[6] Jie *et al* done study on East China Han population and observed association of T1, T2 and F+1 with asthma, however S1, ST+4 and S2 were not observed to be associated with asthma.[8] Similarly, Qu *et al*, found association of 3 SNPs namely, T+1, T1, T2, S1 and V4 with asthma, whereas F+1, T2 and Q-1 were not associated with asthma.[11,38,39]

This study has some limitations that need to be acknowledged. 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[10], butan analysis of haplotypes was not possible because of inadequate haplotype data. Second, this study could not address gene–gene and gene-environment interactions.

In conclusion, to our knowledge, this is the first and most comprehensive genetic meta-analysis to date to find out association of ADAM33 gene polymorphisms with asthma. We found allelic association of S2 and Q-1 SNPs with asthma. The evidence from the meta-analyses supports the notion of a role for the polymorphisms S2, Q-1, and T1 of ADAM33 in susceptibility to Asthma in Asian population.

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Conflict of interest

The authors declare no conflict of interest.

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