

ADAM33 polymorphisms and susceptibility to allergic rhinitis: a meta-analysis

Yu Xu · Ji-Xiang Zhang

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Abstract Several polymorphisms in a disintegrin and metalloproteinase 33 (ADAM33) have been implicated in susceptibility to allergic rhinitis (AR), but the results are inconclusive. This meta-analysis was aimed to clarify the impact of ADAM33 polymorphisms on AR risk. Pubmed, EMBASE and Cochrane library were searched until 11 October 2013 for eligible studies on seven ADAM33 polymorphisms: T1, T2, S1, S2, V4, Q-1 and T+1. Data were extracted, and pooled odd ratios (ORs) as well as 95 % confidence intervals (CIs) were calculated. Six studies with 1,135 AR patients and 1,565 controls were included. It was found that ADAM33 T1 (AG+GG vs. AA, OR 1.47, 95 % CI 1.23–1.75, $I^2 = 94$ %; G vs. A, OR 1.53, 95 % CI 1.32–1.78, $I^2 = 94$ %), T2 (GA+AA vs. GG, OR 1.26, 95 % CI 1.06–1.51, $I^2 = 92$ %; G vs. A, OR 1.27, 95 % CI 1.08–1.50, $I^2 = 92$ %), V4 (CG+GG vs. CC OR 1.35, 95 % CI 1.14–1.59, $I^2 = 95$ %; G vs. C OR 1.28, 95 % CI 1.13–1.44, $I^2 = 96$ %) and Q-1 (GA+AA vs. GG OR 1.55, 95 % CI 1.24–1.95, $I^2 = 74$ %; G vs. C OR 1.46, 95 % CI 1.19–1.79, $I^2 = 73$ %) polymorphisms were significantly associated with AR susceptibility but not S1, S2 and T+1. In Asians, the same result was found. This meta-analysis indicated that ADAM33 T1, T2, V4 and Q-1 polymorphisms may be the risk factors which conferred to AR susceptibility. The differences in ethnicity did not influence the associations

obviously. Gene–gene and gene–environment interactions should be investigated in the future.

Keywords ADAM33 · Polymorphisms · Allergic rhinitis · Meta-analysis

Introduction

Allergic rhinitis (AR), characterized by nasal discharge, blockage, sneezing, and itching, is the most common chronic allergic inflammatory disease of the nasal mucosa that about 10–30 % of adults and up to 40 % of children suffer from [1]. It has been demonstrated that AR is characterized by over secretion of TH2 cytokines, regulatory T (Treg) cells defect and selective eosinophil accumulation following exposure to an allergen in genetically susceptible patients [2–4]. Although AR has been studied extensively, the mechanism of AR is still not well characterized. Genetic epidemiology studies have suggested that AR, which involves the stimulation of the immune cells and the release of many pro-inflammatory mediators, is a poly-genic disease, and genetic susceptibility and environmental factors are involved in the pathogenesis of AR [5]. Many studies have investigated the association between genetic variants with AR susceptibility [6–12], and among them, a disintegrin and metalloproteinase 33 (ADAM33) gene has been highlighted.

ADAM33, a gene located on chromosome 20p13 and a member of the ADAM family, has been extensively studied as a susceptibility gene in bronchial hyperresponsiveness and asthma [13–16]. ADAM33 is a complex molecule whose expression is largely restricted to mesenchymal cells, including fibroblast and smooth muscle, and codes for a protein important for cell fusion, cell adhesion, cell

Y. Xu and J.-X. Zhang contributed equally to this work.

Y. Xu (✉)
Department of Otolaryngology, Renmin Hospital of Wuhan
University, Wuhan 430060, Hubei Province, China
e-mail: xy37138@163.com

J.-X. Zhang
Department of Gastroenterology, Renmin Hospital of Wuhan
University, Wuhan 430060, Hubei Province, China

signalling and proteolysis [17]. 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 [18, 19]. Therefore, clarifying the impact of these genetic variations in the ADAM33 may allow a better understanding of the role of ADAM33 in the pathogenesis of AR.

Recently, a couple of case-control studies across multiethnic groups have assessed the association between ADAM33 polymorphisms (T1, T2, S1, S2, V4, Q-1 and T+1) and AR. However, the results have been proposed for the disparity, including small sample sizes, low statistical power and subjects from different ethnic backgrounds. Therefore, in order to overcome the limitations of these individual studies, resolve inconsistencies, and reduce the likelihood that random errors are responsible for false-positive or false-negative associations, we conducted a meta-analysis of the previously published studies involving the association between ADAM33 polymorphisms (T1, T2, S1, S2, V4, Q-1 and T+1) and AR.

Materials and methods

Search strategy

Pubmed, Embase and Cochrane Library were searched for studies focused on the relationships between the ADAM33 polymorphisms (T1, T2, S1, S2, V4, Q-1 and T+1) and the risk of AR. The latest search was done on 11 October 2013 by two independent reviewers (J.X.Z. and Y.X.). The key words and subject terms used were as follows: “allergic rhinitis” or “AR”, “a disintegrin and metalloprotease 33” or “ADAM33” and “genetic polymorphism”

or “polymorphism” or “variant”. The reference lists in the retrieved studies were also further screened for additional eligible publications. When data were unclear or incomplete, the corresponding author was contacted to clarify data extraction.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria: (1) the study assessed the associations between ADAM33 polymorphisms and AR, (2) controls of included studies were from a healthy population or were subjects without diseases related to AR, (3) the study offered sufficient and complete data to calculate the number of each allele identified. Studies were excluded if: (1) the research did not study anyone of the seven ADAM33 polymorphisms, (2) the genotype frequency was not reported, (3) the article was a review, (4) there was insufficient information to support integrity of the data upon extraction, (5) without control group.

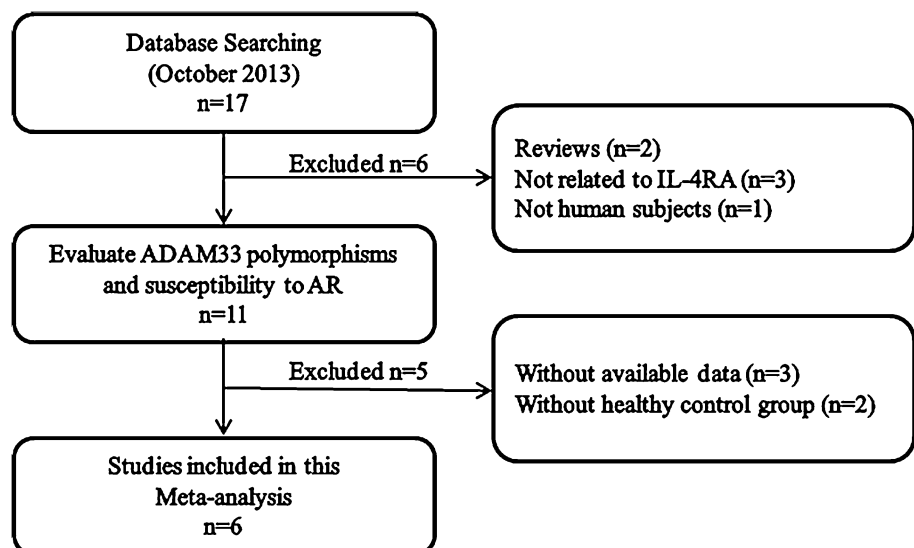
Data extraction

The following information regarding each eligible trial was recorded: year of publication, ethnicity of subjects, sample sizes, and H-W equilibrium of control. Baseline information and data were extracted by two reviewers (J.X.Z. and Y.X.) independently using the same standard. The results were compared and disagreements were resolved by consensus.

Statistical analysis

Variant genotype frequencies were compared between cases and controls. The odds ratio (OR) and 95 % confidence

Fig. 1 The screening process of studies



interval (CI) for the heterozygote and variant homozygote were calculated as compared with the wild type homozygote. In addition to overall comparisons, a subgroup analysis was performed based on ethnicity when adequate data were available. Between-study heterogeneity was estimated using the χ^2 -based Q statistic and I^2 test. When $I^2 > 50\%$ and $P < 0.1$, heterogeneity was considered statistically significant, and random effects model was used to analyze the data subsequently. On the contrary, fixed effects model was chosen. Egger's test was used to assess the publication bias. A χ^2 test was performed to examine HWE, and $P < 0.05$ was considered statistically significant.

All analyses were performed by the Review Manager 5.1 and Stata 12 (Stata Corporation, College Station, Texas) software packages.

Results

Studies included in the meta-analysis

Following the searching strategy, 17 potentially relevant studies were retrieved. According to the inclusion criteria, six studies [20–25] with full-text were included into

Table 1 Characteristics of studies included in the meta-analysis

Reference	Year	Country	Ethnicity	Study design	SNP	Sample size		MAF		P_{HWE} (control)
						AR	Control	AR	Control	
Chen et al. [20]	2012	China	Asian	HB	T1	264	273	0.067	0.057	0.319945
					T2	265	274	0.089	0.069	0.2174427
					S2	265	274	0.228	0.164	0.8635363
					V4	264	274	0.545	0.509	0.0524589
					T+1	265	273	0.089	0.059	0.3036436
Cheng et al. [21]	2004	Japan	Asian	PB	T1	95	95	0.053	0.179	0.1538679
					T2	95	95	0.058	0.179	0.1538679
					S2	94	95	0.176	0.295	0.5363995
					T+1	95	95	0.053	0.147	0.0920598
Miyake et al. [22]	2010	Japan	Asian	HB	T1	393	767	0.141	0.147	0.4990097
					T2	392	767	0.149	0.159	0.7043911
					S2	392	767	0.276	0.269	0.2200102
					V4	393	767	0.313	0.368	0.9938248
					Q-1	393	767	0.137	0.118	0.4205112
					T+1	393	767	0.139	0.147	0.2109655
Suet al. [23]	2008	China	Asian	PB	T1	128	151	0.348	0.129	0.0725186
					T2	128	151	0.094	0.040	0.6111185
					S1	128	151	0.109	0.036	0.6422877
					V4	128	151	0.406	0.146	0.0676682
					Q-1	128	151	0.063	0.036	0.6422877
					T+1	128	151	0.230	0.136	0.0535658
Zhang et al. [24]	2009	China	Asian	PB	T1	135	151	0.448	0.129	0.0725186
					T2	135	151	0.267	0.040	0.6,111,185
					S1	135	151	0.111	0.136	0.0535658
					V4	135	151	0.444	0.146	0.0676682
					Q-1	135	151	0.133	0.036	0.6422877
					T+1	135	151	0.081	0.136	0.0535658
Zihlif et al. [25]	2013	Jordan	Caucasian	HB	T1	120	128	0.250	0.180	0.9365228
					T2	120	128	0.250	0.190	0.859232
					S1	120	128	0.060	0.050	0.5779293
					S2	120	128	0.450	0.320	0.9569988
					V4	120	128	0.220	0.180	0.9365228
					Q-1	120	128	0.190	0.130	0.9203992
					T+1	120	128	0.250	0.180	0.9365228

this meta-analysis and 11 studies were excluded (Fig. 1). All six studies [20–25] reported the associations between ADAM33 T1 polymorphism and AR, T2 with AR, and T+1 with AR. Three [23–25] examined the associations between ADAM33 S1 polymorphism and AR. Four studies [20–22, 25] examined the association between ADAM33 S2 polymorphism and AR. Five studies [20, 22–25] reported the association between ADAM33 V4 polymorphism and AR and four studies [22–25] examined the association between ADAM33 Q–1 polymorphism and AR (Table 1). The distribution of genotypes in the controls

was consistent with Hardy–Weinberg equilibrium for all selected studies.

ADAM33 polymorphisms and AR risk

A summary of the meta-analysis findings concerning associations between ADAM33 polymorphisms and AR risk is shown in Tables 2 and 3.

Six studies [20–25] with 1,135 cases and 1,565 controls, reported associations between ADAM33 T1 polymorphism and AR susceptibility. As the results shown that ADAM33

Table 2 Pooled analysis for the associations between the ADAM33 polymorphisms with the risk of AR

SNP	N	Comparison	Test of association		Test of heterogeneity		Publication bias <i>P</i> value
			OR (95 % CI)	<i>P</i> value	<i>P</i> value	<i>I</i> ² (%)	
T1	6	AG vs. AA	1.34 (1.11–1.60)	0.002	0.000	92	0.514
		GG vs. AA	3.56 (2.33–5.44)	0.000	0.000	82	0.939
		AG+GG vs. AA	1.47 (1.23–1.75)	0.000	0.000	94	0.772
		GG vs. AG+AA	2.88 (1.87–4.44)	0.000	0.010	70	0.917
		G vs. A	1.53 (1.32–1.78)	0.000	0.000	94	0.917
T2	6	GA vs. GG	1.21 (1.01–1.46)	0.040	0.000	92	0.566
		AA vs. GG	2.04 (1.19–3.51)	0.010	0.060	55	0.174
		GA+AA vs. GG	1.26 (1.06–1.51)	0.010	0.000	92	0.517
		AA vs. GA+GG	1.91 (1.11–3.31)	0.020	0.140	43	0.123
		A vs. G	1.27 (1.08–1.50)	0.003	0.000	92	0.465
S1	3	GA vs. GG	1.33 (0.92–1.93)	0.130	0.005	81	0.510
		AA vs. GG	1.04 (0.38–2.83)	–	–	–	–
		GA+AA vs. GG	1.33 (0.92–1.93)	0.130	0.005	81	0.510
		AA vs. GA+GG	1.10 (0.41–1.19)	–	–	–	–
		A vs. G	1.29 (0.91–1.84)	0.150	0.007	80	0.499
S2	4	CG vs. CC	1.15 (0.95–1.39)	0.140	0.005	77	0.652
		GG vs. CC	1.31 (0.93–1.85)	0.120	0.003	78	0.780
		CG+GG vs. CC	1.17 (0.98–1.40)	0.080	0.001	82	0.803
		GG vs. CG+CC	1.21 (0.87–1.69)	0.260	0.020	71	0.675
		G vs. C	1.14 (0.99–1.32)	0.060	0.002	85	0.909
V4	5	CG vs. CC	1.26 (1.05–1.50)	0.010	0.000	94	0.056
		GG vs. CC	1.52 (1.18–1.96)	0.001	0.000	92	0.100
		CG+GG vs. CC	1.35 (1.14–1.59)	0.001	0.000	95	0.071
		GG vs. CG+CC	1.39 (1.10–1.75)	0.006	0.000	85	0.110
		G vs. C	1.28 (1.13–1.44)	0.000	0.000	96	0.074
Q–1	4	GA vs. GG	1.57 (1.25–1.97)	0.000	0.010	73	0.233
		AA vs. GG	1.34 (0.60–2.98)	0.480	0.420	0	–
		GA+AA vs. GG	1.55 (1.24–1.95)	0.000	0.009	74	0.211
		AA vs. GA+GG	1.25 (0.56–2.78)	0.580	0.470	0	–
		A vs. G	1.46 (1.19–1.79)	0.000	0.010	73	0.181
T+1	6	GA vs. GG	0.97 (0.80–1.17)	0.730	0.000	81	0.588
		AA vs. GG	1.74 (1.00–3.02)	0.050	0.250	25	0.060
		GA+AA vs. GG	1.01 (0.84–1.21)	0.920	0.000	83	0.682
		AA vs. GA+GG	1.70 (0.98–2.95)	0.060	0.330	13	0.183
		A vs. G	1.05 (0.90–1.24)	0.530	0.000	82	0.713

T1 polymorphism was significantly associated with AR susceptibility (Table 2; Fig. 2). Significant association was also found in Asian (Table 3).

In addition, there were six studies [20–25] containing 1,135 cases and 1,566 controls, examined associations between ADAM33 T2 polymorphism and AR susceptibility. It was found that ADAM33 T2 polymorphism was significantly associated with AR susceptibility (Table 2; Fig. 3). Positive result was also found in Asian (Table 3).

Three studies [23–25] with 383 cases and 430 controls, examined associations between ADAM33 S1

polymorphism and AR susceptibility. It was found that ADAM33 S1 polymorphism was not associated with AR susceptibility (Table 2). Negative result was also found in Asian (Table 3).

There were 871 cases and 1,264 controls in four studies [20–22, 25], examined the association between ADAM33 S2 polymorphism and AR. ADAM33 S1 polymorphism was found not associated with AR susceptibility (Table 2). Same result was also found in Asian (Table 3).

Meanwhile, five studies [20, 22–25] containing 1,040 cases and 1,471 controls, reported the association between

Table 3 Subgroup analysis for the associations between the IL-4RA polymorphisms with the risk of AR

Comparison	Subgroup	Test of association		Test of heterogeneity		Subgroup difference		
		OR (95 % CI)	<i>P</i> value	<i>P</i> value	<i>I</i> ² (%)	<i>P</i> value	<i>I</i> ² (%)	
T1								
AG+GG vs. AA	Asian	1.45 (1.21, 1.75)	0.000	0.000	95	0.790	0	
	Caucasian	1.57 (0.93, 2.62)	0.090	–	–			
G vs. A	Asian	1.54 (1.31, 1.80)	0.000	0.000	96	0.970	0	
	Caucasian	1.52 (0.99, 2.35)	0.060	–	–			
T2								
GA+AA vs. GG	Asian	1.23 (1.02, 1.49)	0.030	0.000	94	0.470	0	
	Caucasian	1.51 (0.90, 2.52)	0.120	–	–			
A vs. G	Asian	1.25 (1.05, 1.49)	0.010	0.000	94	0.620	0	
	Caucasian	1.41 (0.92, 2.16)	0.070	–	–			
S1								
GA+AA vs. GG	Asian	1.35 (0.89, 2.05)	0.160	0.010	91	0.910	0	
	Caucasian	1.28 (0.57, 2.88)	0.560	–	–			
A vs. G	Asian	1.30 (0.88, 1.93)	0.190	0.002	90	0.940	0	
	Caucasian	1.26 (0.57, 2.78)	0.570	–	–			
S2								
CG+GG vs. CC	Asian	1.09 (0.90, 1.32)	0.380	0.002	84	0.030	78.1	
	Caucasian	2.00 (1.18, 3.37)	0.010	–	–			
G vs. C	Asian	1.06 (0.91, 1.24)	0.450	0.001	86	0.010	83.2	
	Caucasian	1.74 (1.20, 2.50)	0.003	–	–			
V4								
CG+GG vs. CC	Asian	1.35 (1.13, 1.61)	0.001	0.000	97	0.930	0	
	Caucasian	1.32 (0.78, 2.22)	0.030	–	–			
G vs. C	Asian	1.27 (1.13, 1.44)	0.000	0.000	97	0.950	0	
	Caucasian	1.29 (0.83, 2.01)	0.250	–	–			
Q–1								
GA+AA vs. GG	Asian	1.54 (1.21, 1.97)	0.000	0.000	96	0.860	0	
	Caucasian	1.62 (0.93, 2.82)	0.090	–	–			
A vs. G	Asian	1.44 (1.15, 1.81)	0.001	0.004	82	0.780	0	
	Caucasian	1.56 (0.96, 2.54)	0.070	–	–			
T+1								
GA+AA vs. GG	Asian	0.95 (0.78, 1.15)	0.590	0.000	84	0.070	68.5	
	Caucasian	1.57 (0.93, 2.62)	0.090	–	–			
A vs. G	Asian	0.99 (0.83, 1.18)	0.930	0.000	84	0.070	69.1	
	Caucasian	1.52 (0.99, 2.35)	0.060	–	–			

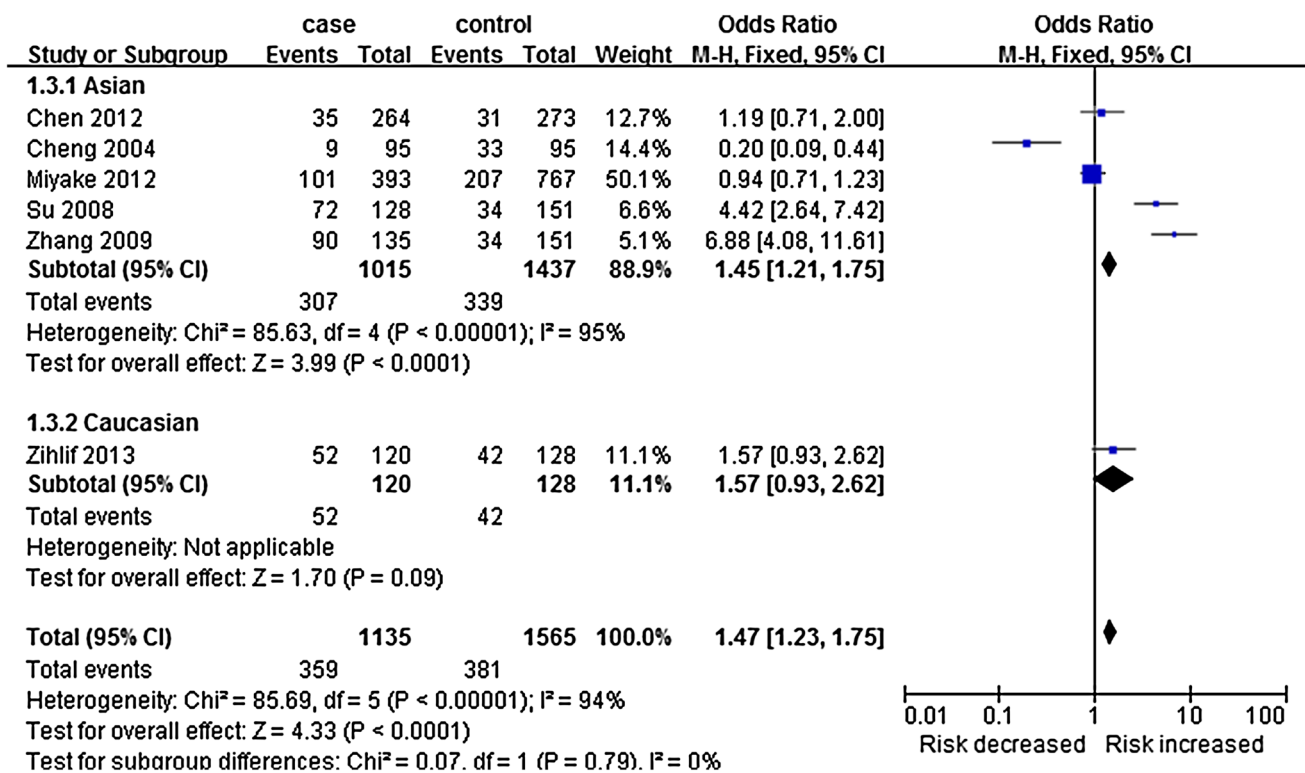


Fig. 2 Meta-analysis of the association between ADAM33 T1 polymorphism and AR for AG+GG vs. AA

ADAM33 V4 polymorphism and AR. It was found that ADAM33 V4 polymorphism was associated with AR susceptibility (Table 2; Fig. 4). Negative result was also found in Asian (Table 3).

Four studies [22–25] with 776 cases and 1,197 controls, examined the association between ADAM33 Q–1 polymorphism and AR. ADAM33 Q–1 polymorphism was associated with AR susceptibility (Table 2 and Fig. 5). Negative result was also found in Asian (Table 3).

Also, all six studies [20–25] with 1,136 cases and 1,565 controls reported associations between ADAM33 T+1 polymorphism and AR susceptibility. It was found that ADAM33 T+1 polymorphism was not significantly associated with AR susceptibility. Same result was found in Asian (Table 3).

Test of heterogeneity and publication bias

Heterogeneity of the included studies pertaining to each polymorphism is presented in Tables 2 and 3. Except for GG vs. AG+AA ($I^2 = 43\%$, $P = 0.140$) for T2, AA vs. GG ($I^2 = 0\%$, $P = 0.420$) and AA vs. GA+GG ($I^2 = 0\%$, $P = 0.470$) for Q–1, AA vs. GG ($I^2 = 25\%$, $P = 0.250$) and GG vs. AG+AA ($I^2 = 13\%$, $P = 0.330$) for T+1, there was significant heterogeneity for all the rest comparisons.

As indicated by Egger's test, there was no potential publication bias for all the comparisons (Table 2).

Discussion

AR is a chronic inflammatory disease that 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 [26, 27]. It is induced by an IgE-mediated reaction, following exposure to an allergen. In addition, it has been demonstrated that airway angiogenesis played an important role in the pathogenesis of rhinitis. Recently, many case-control studies have identified a number of single nucleotide polymorphisms (SNPs) and chromosomal regions potentially associated with AR, and up to date, more than 100 SNPs have been reported to be associated with this disease [28].

ADAM33, which maps to human chromosome 20p13 and consists of 22 exons, was recently identified to be a bronchial hyperresponsiveness and asthma susceptibility gene [14, 29]. ADAM33 mRNA expression was found to be elevated in the lungs of a murine model of allergen-induced chronic airway inflammation [30]. Angiogenesis is a fundamental process that supports many aspects of

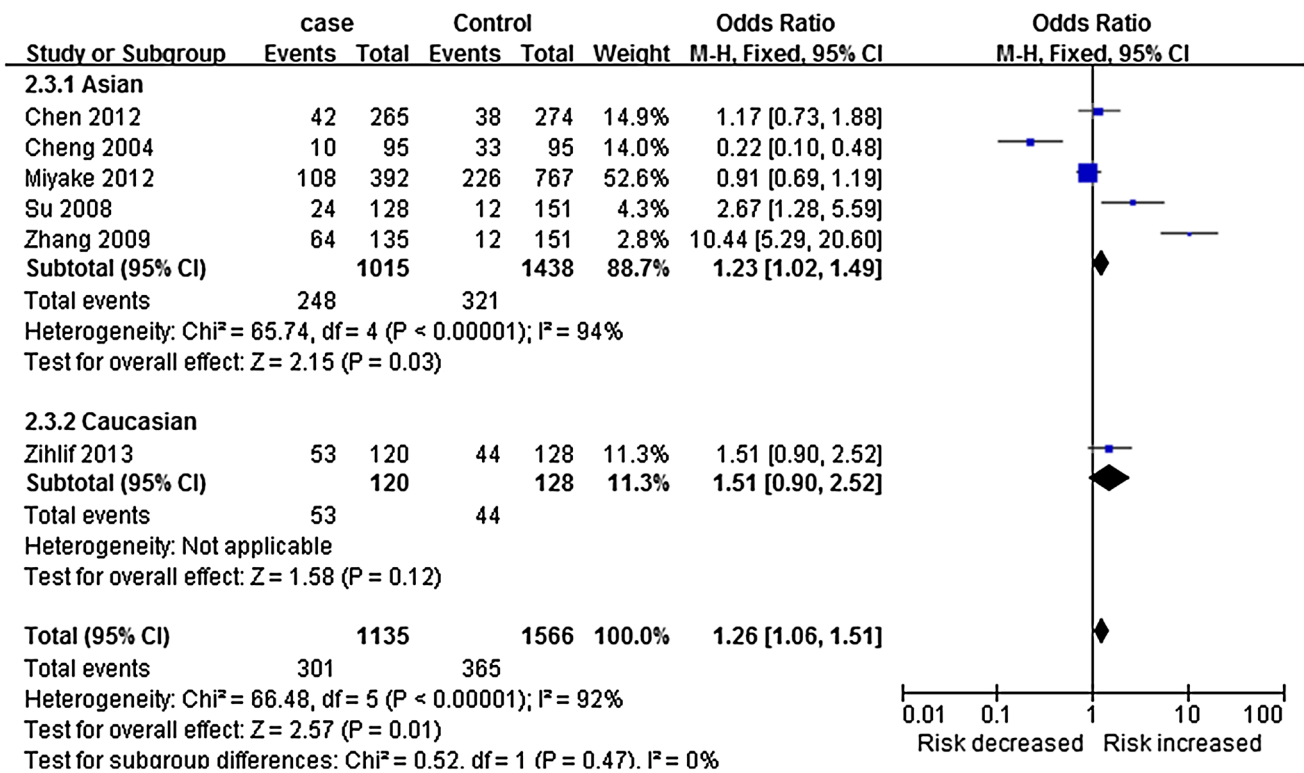


Fig. 3 Meta-analysis of the association between ADAM33 T2 polymorphism and AR for GA+AA vs. GG

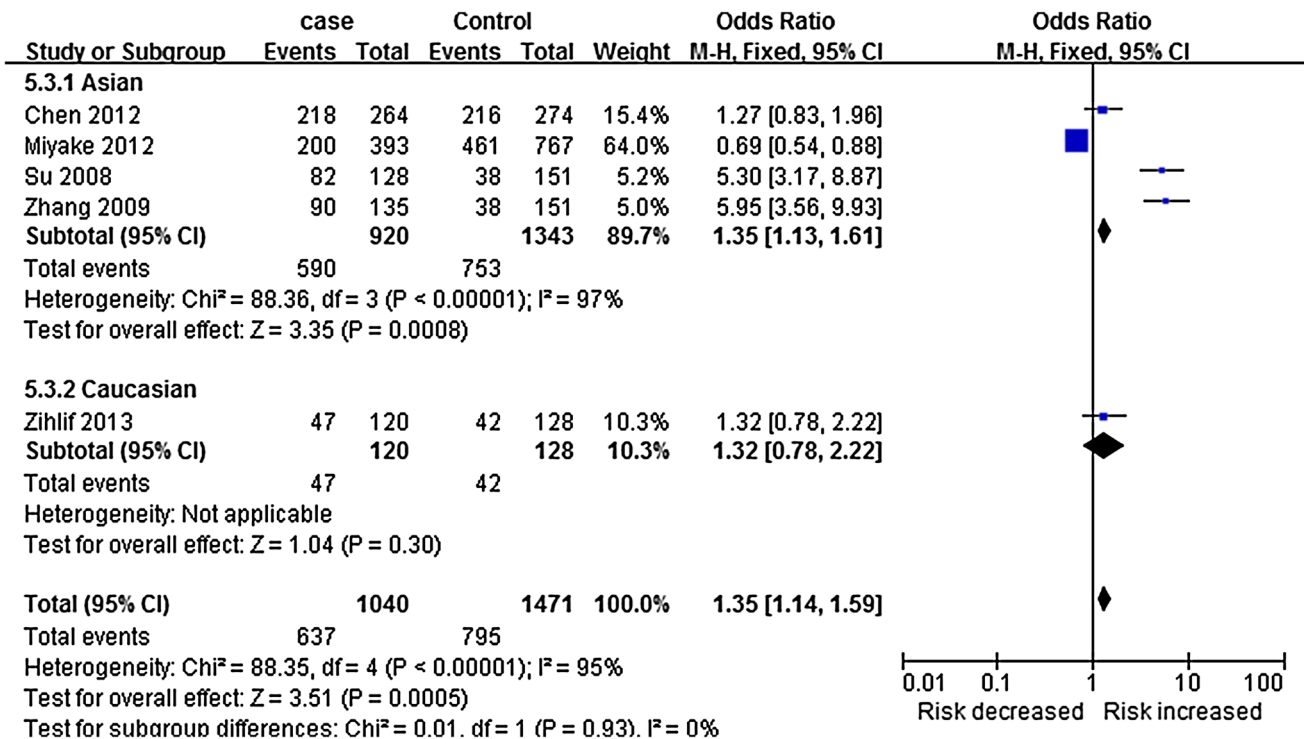


Fig. 4 Meta-analysis of the association between ADAM33 V4 polymorphism and AR for CG+GG vs. CC

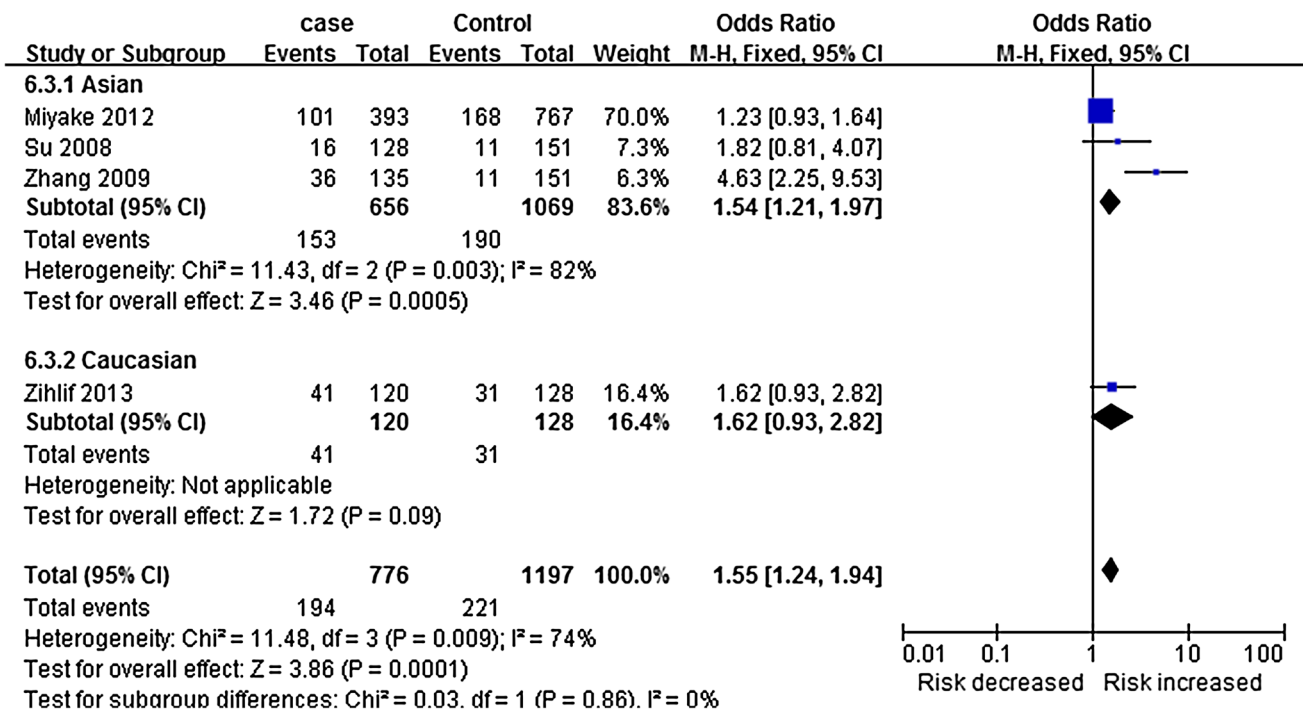


Fig. 5 Meta-analysis of the association between ADAM33 Q–1 polymorphism and AR for GA+AA vs. GG

tissue inflammation and remodeling. A laboratory study has demonstrated that a soluble form of ADAM33 containing the catalytic domain causes rapid induction of endothelial cell differentiation in vitro and angiogenesis both ex vivo and in vivo, suggesting that ADAM33 acts as a remodeling gene [31]. So far, several AR-related loci located in ADAM33 have been identified, but because of the differences, including sample sizes, statistical power and ethnic backgrounds, all the conclusions are not unanimous. So performing a meta-analysis to evaluate the associations between ADAM33 polymorphisms and AR is necessary.

Our meta-analysis, including six studies concerning T1, T2, S1, S2, V4, Q–1 and T+1, is the first quantitative evaluation with respect to the associations between ADAM33 polymorphisms and AR risk. In the seven SNPs, 10918G/C (SNP S2, Gly717Gly) in exon 19 encoding the transmembrane domain, 12433T/C (SNP T1, Met764Thr) and 12462C/T (SNP T2, Pro774Ser) in exon 20 encoding the cytoplasmic domain and 12540C/T (SNP T+1) in intron 20. It was indicated by our meta-analysis that ADAM33 T1, T2, V4 and Q–1 polymorphisms were significantly associated with AR susceptibility, but positive associations were not found between S1, S2 and T+1 with AR. According to the subgroup analysis by ethnicity, the results were the same.

Though we attempted to minimize the likelihood of bias by developing a detailed protocol before initiating the study, some insurmountable limitations of this meta-analysis may affect the results and even the subsequent conclusions.

First, because of incomplete raw data or publication limitations, several relevant studies could not be included in this meta-analysis. Second, the numbers of subjects and studies included in the meta-analysis were small, and may not have been sufficient to reveal the associations between ADAM33 polymorphisms and AR. Third, because not all necessary information could be obtained from most included studies, relevant stratifications could not be made for many studies.

In conclusion, this meta-analysis indicated that ADAM33 T1, T2, V4 and Q–1 polymorphisms may be the risk factors which conferred to AR susceptibility. The differences in ethnicity did not influence the associations obviously. Because AR-related genetic factors may interfere with non-genetic risk factors, such as environment and diet, future studies should therefore be stratified in these ways.

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