Asthma susceptible genes in children: A meta-analysis

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Research

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Abstract

Background: During the last decade, a number of studies have evaluated the potential association between some genetic polymorphisms and childhood asthma risk, however, the results of published studies appeared conflicts. The aim of the present study was to investigate association between genetic polymorphisms and pediatric asthma.

Methods: Relevant studies were searched in PubMed, Embase, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang and Weipu database. Pooled odds ratios (OR) with 95% confidence interval (CI) were calculated to access the strength of the associations.

Results: 45 case-control studies were finally included in this meta-analysis. Eighteen SNPs were identified. Ten polymorphisms were found to be associated with asthma risk: *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* F+1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST+4, *ORMDL3* rs7216389, *VDR* Apa $\square$, *VDR* Fok $\square$, *VDR* Bsm $\square$. After subgroup analysis, *IL-13* +2044G/A, *ADAM33* T2, *ADAM33* T1, *VDR* Apa $\square$, *VDR* Bsm $\square$ polymorphisms were associated with increased risk of asthma among Asian populations. *IL-4* -590C/T polymorphisms may be related to asthma risk in Chinese children.

Conclusions: This meta-analysis found that *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* F+1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST+4, *ORMDL3* rs7216389, *VDR* Apa $\square$, *VDR* Fok $\square$ and *VDR* Bsm $\square$ polymorphisms might be risk factors for childhood asthma. Further study with large population and more ethnicities is needed to estimate the associations.

Introduction

Bronchial asthma is one of the most prevalent chronic diseases in childhood. It is a complex disease characterized by reversible airway obstruction and chronic inflammation¹. Asthma exacerbation is an important cause of childhood morbidity and hospitalization. The prevalence of asthma in children is higher than that in adults and it continues to increase worldwide, particularly in low- and middle-income countries^{2,3}. About 14.2% of children worldwide experienced asthma symptoms. The global mortality rate for childhood asthma ranges 0 to 0.7 per 100,000 population⁴⁻⁶. Lifetime prevalence reaches 14% in children. Asthma seriously affects childhood health and imposes extremely high medical costs on families and society. There is an association between childhood asthma and adult COPD (Chronic obstructive pulmonary disease). Children with severe asthma have a high risk of developing adult COPD⁷. Due to the heterogeneity of asthma, there are differences in the clinical manifestations of children at different ages, which may make it harder to diagnose asthma in children⁸. Both genetic and environmental factors contribute to inception and evolution of asthma. Genes play a greater role in pediatric asthma than adults, a genome-wide association study (GWAS) found that the genes associated with childhood asthma are almost three times that of adults⁹. GWASs have identified several regions associated with asthma⁶. In recent years, the exploration of genetic susceptibility to asthma has become an important subject worldwide. However, some results remain largely inconsistent, even contradictory. Therefore, we carried out a meta-analysis to assess association between genetic polymorphisms and pediatric asthma.

Materials And Methods

Search strategy

We used electronic databases of English (PubMed, Embase, Web of Science) and Chinese (China National Knowledge Infrastructure (CNKI), Wanfang, Weipu) to search relevant articles published between January 2010 and January 2020. The following Medical Subject Heading (MeSH) terms were used for search: "asthma", "asthmatic", "gene", "genetic", "case-control studies", "pediatric", "childhood". Corresponding Chinese words were used in the Chinese database. The language was no restricted.

Inclusion and exclusion Criteria

Inclusion criteria included: 1) articles on the relationship between genetic variants and pediatric asthma (age $\leq$ 18 years); 2) articles published in journals; 3) the patients were clinically diagnosed with asthma; 4) allele and genotype distributions were available to estimate an odds ratio (OR) with 95% confidence interval (CI) and P value in control and case groups; 5) genotype distributions of control group had to be in Hardy-Weinberg Equilibrium (HWE, $P > 0.05$); 6) each polymorphism should be studied in at least three case-control studies; 7) gene polymorphism characterized as A/B, including genotypes: AA, AB and BB. 8) when the author published multiple articles on the same topic, only the latest full-text articles were included in the final analysis.

Exclusion criteria included: 1) conference papers, meta-analysis or review articles; 2) with duplicated data; 3) polymorphisms with data less than three case-control; 4) not present the usable data; 5) unavailable full-text.

Data extraction and quality Assessment

Two researchers independently estimated the literature, extracted the data, and cross-checked based on the inclusion and exclusion criteria. Any disagreement was resolved by discussing and negotiating with a third researcher. In literature screening, we first read the title of the article to exclude obviously irrelevant literature, and then read the abstract and the full text to determine whether to include. Data extraction includes: the name of first author, publication year, country, ethnicity, mean age, number of cases and controls, genotyping methods and allele and genotype frequencies in cases and controls. The quality of each study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). Studies scoring 0–3, 4–6, or 7–9 were defined as low-, moderate-, or high-quality study, respectively. The results of study quality assessment were shown in Table 1.

Table 1
Main characteristics of included studies in this meta-analysis

Study	Country	Ethnicity	Mean age		Total		Genotyping	Polymorphisms	Quality scores
			Cases Control		Case Controls		Methods		
Awasthi 2011	Indian	Asian	74.39 ± 45.7 m (1-15y)	73.61 ± 42.56 m (1-15y)	211	137	PCR-RFLP	ADAM33 F + 1, V4, ST + 4, S2	7
Qu 2011	China	Asian	7.74 ± 2.78 (8-13)	7.52 ± 2.95 (8-13)	412	397	PCR-RFLP	ADAM33 F + 1, T + 1, T2, T1, V4	8
Wang 2017	China	Asian	3-15	3-15	197	120	PCR-RFLP	ADAM 33 F + 1	7
Fan 2015	China	Asian	5.27-1.93 (2-10)	5.68-2.17 (3-12)	120	105	PCR-RFLP	ADAM 33 F + 1, T1, S2	8
Shalaby 2015	Egypt	African	8.5 (± 3.6) (3-14)	8.8 (± 2.6) (4-13)	400	200	PCR-RFLP	ADAM33 F + 1, ST + 4	6
Li 2014	China	Asian	10.4 ± 2.9 (3.1-14.6)	3.1-14.6	299	311	PCR-RFLP	ADAM33 V4, T2, S2, S1, T1	6
Zihlif 2014	Jordan	Asian	5.96-4.63	7.53-4.83	107	115	PCR-RFLP	ADAM33 T1, T2, V4, S2	6
Zhao 2012	China	Asian	14.2 ± 3.4 (3.1-14.8)	14.5 ± 3.5 (3.3-14.9)	110	144	PCR-RFLP	ADAM33 T2, V4	6
Yu 2018	China	Asian	6.26 ± 2.06 (5-12)	6.19 ± 2.03	105	98	Sequencing	ADAM33 ST + 4	7
Ding 2013	China	Asian	6.62 ± 1.90 (1-14)	5.86 ± 2.11 (0.78-14)	90	82	PCR-RFLP	IL-13 + 2044G/A	7
Guo 2017	China	Asian	5.4 ± 1.8 (1-13)	6.3 ± 2.1 (3-14)	80	112	PCR-RFLP	IL-13 + 2044G/A IL-13 -1112C /T	8
Zhang 2016	China	Asian	5.68 ± 3.33	4.85 ± 3.69	153	103	Mass Array	IL-13 + 2044G/A	8

m: month, y: year, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, AS-PCR Allele-specific PCR

Study	Country	Ethnicity	Mean age		Total		Genotyping	Polymorphisms	Quality scores
			Cases Control		Case Controls		Methods		
Narozna 2016	Poland	Caucasian	11.5 ± 3.6	12.1 ± 33.4	177	194	TaqMan	IL-13 + 2044G/A IL-4 -590C/T	6
Martínez 2015	Mexico	Mestizo	10.8 ± 2.9	NA	421	430	TaqMan	IL-13 -1112C /T ADRB2 -46G /A	6
Dixit 2014	India	Asian	6.29 ± 3.28 (1–15)	6.08 ± 3.22 (1–15)	275	275	PCR-RFLP	IL-13 -1112C /T IL-4 -590C /T	7
Liao 2014	China	Asian	6.30 ± 3.39	4.96 ± 3.61	300	200	PCR-RFLP	IL-13 -1112C /T IL-4 -590C/T	7
Huang 2013	China	Asian	48.6 ± 43.2 m	40.9 ± 41.5	168	188	Mass Array	ORMDL3 rs7216389	7
Yang 2012	China	Asian	5.872 ± 2.543	6.038 ± 2.526	152	190	Mass Array	ORMDL3 rs7216389	6
Wei 2016	China	Asian	6.02 ± 1.98	6.31 ± 2.04	128	100	Mass Array	ORMDL3 rs7216389	7
Pu 2013	China	Asian	5.8 ± 2.9(3–12)	5.6 ± 2.6	96	96	PCR-RFLP	IL-13 + 1923	7
Ramphul 2014	Mixed	Mauritian/Asian	3–12	18–22	M: 193 C: 192	M:189 C:192	PCR-RFLP	IL-13 + 1923 IL-4 -590C/T ADRB2 -46G /A	7
Zeng 2015	China	Asian	6. 60 ± 3. 40	4. 91 ± 3. 73	250	200	PCR-RFLP	IL-4 -590C/T	7

m: month, y: year, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, AS-PCR Allele-specific PCR

Study	Country	Ethnicity	Mean age		Total		Genotyping Methods	Polymorphisms	Quality scores
			Cases	Control	Case	Controls			
Zhang 2010	China	Asian	10.3 ± 1.5 (6–13)	10.1 ± 1.5 (6–13)	291	668	PCR-RFLP	IL-4 -590C/T	7
Wu 2019	China	Asian	6.8 ± 2.7 (3–12)	6.6 ± 2.5 (3–12)	160	160	PCR-RFLP	IL-13 -1112C /T IL-4 -590C/T	7
Li 2014	China	Asian	8.4 ± 2.7 (3–12)	7.9 ± 3.2 (3–12)	500	523	PCR-RFLP	IL-13 -1112C /T IL-4 -590C/T	7
Lin 2012	China	Asian	4.4 ± 2.3 (1.4– 13)	7.7 ± 2.5 (3–14)	72	102	PCR-RFLP	IL-4 -590C/T	8
Huang 2010	China	Asian	6.57 ± 2.76 (2–13)	7.46 ± 2.94 (3–14)	100	122	PCR-RFLP	IL-4 -590C/T	6
Yan 2015	China	Asian	6 ± 2. 8 (6 m– 14y)	7 ± 2.1 (4–14)	34	30	PCR-RFLP	IL -4 – 590C/T	7
Karam 2013	Egypt	African	10.3 ± 2.4	9.8 ± 2.8	90	110	AS-PCR	ADRB2 -46G /A ADRB2 -79G/C	6
Abdullah 2011	Saudi Arabia	Caucasian	10.4 ± 4.6	12.6 ± 4.2	73	85	PCR-RFLP	ADRB2 -46G /A ADRB2 -79G/C	7
Zheng 2012	China	Asian	3.5	3.8	198	110	StepOnePlus/TaqMan	ADRB2 -46G /A	8
Feng 2018	China	Asian	5.8 ± 2.8 (2–12)	6.3 ± 3. 1 (2–12)	173	166	Taqman	ADRB2 -46G /A ADRB2 -79G/C	8

m: month, y: year, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, AS-PCR Allele-specific PCR

Study	Country	Ethnicity	Mean age		Total		Genotyping Methods	Polymorphisms	Quality scores
			Cases	Control	Case	Controls			
Isaza 2012	Colombia	Mestizo	(6–17)	(6–17)	109	137	Sequencing	ADRB2 -46G /A ADRB2 -79G/C	9
Qi 2014	China	Asian	1.1– 14	2–14	120	117	PCR-RFLP	ADRB2 -79G/C	7
Tian 2016	China	Asian	5.6 ± 10.3 (0.75- 16)	5.2 ± 9.8 (2–14)	298	304	TaqMan	ADRB2 -46G /A ADRB2 -79G/C	8
Kilic 2019	Turkey	Caucasian	9.5 ± 2.8 (5–16)	9.5 ± 2.5 (5–14)	80	100	StepOnePlus/TaqMan	VDR Apa ¹ , TaqI, FokI	8
Maalmi 2013	Tunisia	African	9.1 (4–16)	9.5 (2– 16)	155	225	PCR-RFLP	VDR Apa ¹ , TaqI, FokI, Bsm ¹	7
Mo 2015	China	Asian	NA	NA	71	71	PCR-RFLP	VDR Apa ¹ , Bsm ¹	7
Zhu 2019	China	Asian	8.76 ± 1.22	8.60 ± 1.16	97	100	Sequencing	VDR FokI, Bsm ¹	8
Ismail 2013	Egypt	African	8.6 ± 2.7	7.8 ± 2.6	51	33	TaqMan	VDR FokI	6
Zhao 2015	China	Asian	3.14 ± 1.07 (2–6)	3.37 ± 1.04 (2–6)	40	40	Sequencing	VDR Apa ¹ , TaqI, FokI, Bsm ¹	7
Ma 2014	China	Asian	11	10.6	60	60	PCR-RFLP	VDR Apa ¹ , TaqI, FokI, Bsm ¹	7
Zhang 2010	China	Asian	7.1 ± 2.3	7.1 ± 1.6	118	160	PCR-RFLP	CTLA-4 ¹ 49A/G	7
Wang 2014	China	Asian	8 m- 10y	9 m-10y	40	40	Sequencing	CTLA-4 ¹ 49 A/G	8
Zhang 2012	China	Asian	1–10	3–7	26	30	PCR-RFLP	CTLA-4 ¹ 49 A/G	6

m: month, y: year, PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism, AS-PCR Allele-specific PCR

Statistical analysis

The strength of the association between each SNP and pediatric asthma was estimated by odds ratio (OR) with 95% confidence interval (CI). The pooled OR was performed using the Z test. The allelic model, homozygous model, heterozygous model, dominant model and

recessive model were examined to evaluate effect of each SNP. The between-study heterogeneity was assessed with χ^2 -based Q-test and I^2 statistic was calculated to observe between-study variability that was due to heterogeneity rather than chance. If $I^2 < 50\%$ and $P \geq 0.1$, the pooled OR was calculated by the fixed-effects model; otherwise, a random-effects model was applied. Subgroup analysis based on ethnicity were preformed to investigated possible causes of heterogeneity. For each synthesized data, sensitivity analysis was conducted by systematically omitted each study in turn to determine the impact on the heterogeneity test and assess the stability of the overall results. Potential publication bias was estimated by using funnel plots, Begg's test and Egger's test. All statistical analyses were performed using Revman software (version 5.3) and Stata software (version 15.1). A P value < 0.05 was considered statistically significant, while the level of 0.10 were used for the heterogeneity test.

Results

Study Inclusion and Characteristics

The flow chart of the selection process is shown in Fig. 1. Briefly, a total of 1913 articles were identified after initial search, of which, 868 duplicate articles were removed. After screening the titles and abstracts, 270 articles were selected. The 270 full-text articles were evaluated based on inclusive and exclusive criteria. Finally, 45 articles were included in the meta-analysis, including 7592 asthma patients and 7671 controls. The included studies were published between 2010 and 2020 and were conducted in ten countries: China, Indian, Egypt, Jordan, Poland, Mexico, Saudi Arabia, Colombia, Turkey and Tunisia. A total of 18 polymorphisms in 7 genes were identified for data synthesis: *IL-13* + 2044G/A (rs20541)¹⁰⁻¹⁴, *IL-13* -1112C/T(rs1800925)^{11,13,15-18}, *IL-13* + 1923C/T (rs1295686)^{19,20}, *IL-4* -590C/T (rs2243250)^{12,15-18,20-25}, *ADRB2* -46 G /A(rs1042713)^{11,20,26-31}, *ADRB2* -79G/C (rs1042713)^{26,28-32}, *ADAM33* F + 1(rs511898)³³⁻³⁶, *ADAM33* V4 (rs2787094)^{33,34,37-39}, *ADAM33* S2(rs528557)^{33,35,38,39}, *ADAM33* T2 (rs2280090)^{34,37-39}, *ADAM33* T1(rs2280091)^{34,35,38,39}, *ADAM33* ST + 4 (rs44707)^{33,40,41}, *ORMDL3* rs7216389⁴²⁻⁴⁴, *VDR* ApaⅡ(rs7975232)⁴⁵⁻⁴⁹, *VDR* FokⅠ(rs2228570)^{45-47,49-51}, *VDR* BsmⅠ(rs1544410)^{46-49, 51}, *VDR* TaqⅠ(rs731236)^{45-47, 49}, and *CTLA-4* + 49 G/A (rs231775)⁵²⁻⁵⁴. The detailed characteristics of included studies are given in Table 1.

Results of meta-analysis

The results of meta-analyses of the association between each polymorphism and the risk of pediatric asthma in the total population and in Asian are shown in Table 2.

Table 2
Meta-analysis of the association between SNPs of 18 genes and pediatric asthma risk

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity			Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z	p
IL-13 + 2044G/A rs20541	A vs G	5	1.52	1.15–2.01	0.004	R	0.01	69	2.20	0.03
	AA vs GG		1.73	0.90–3.35	0.10	R	0.02	66	0.73	0.46
	GA vs GG		1.79	1.18–2.72	0.006	R	0.01	69	1.71	0.09
	GA + AA vs GG		1.80	1.14–2.28	0.01	R	0.002	76	1.71	0.09
	AA vs GA + GG		0.99	0.78–1.25	0.94	F	0.13	44	1.22	0.22
Asians	A vs G	3	1.93	1.51–2.48	<0.00001	F	0.49	0	-	-
	GA + AA vs GG		2.56	1.83–3.58	<0.00001	F	0.30	17	-	-
IL-13 -1112C/T rs1800925	T vs C	6	0.63	0.16–2.56	0.52	R	<0.00001	99	0.75	0.45
	TT vs CC		1.27	0.61–2.63	0.53	R	<0.00001	86	0.75	0.45
	CT vs CC		1.19	0.72–1.97	0.49	R	<0.00001	90	0.00	1.00
	CT + TT vs CC		1.18	0.71–1.96	0.59	R	<0.00001	92	1.13	0.26
	TT vs CT + CC		1.11	0.59–2.09	0.75	R	<0.0001	83	0.75	0.45
Asians	T vs C	5	1.16	0.68–1.96	0.59	R	<0.00001	93	-	-
	CT + TT vs CC		1.28	0.67–2.43	0.45	R	<0.00001	93	-	-
IL-13 + 1923C/T rs1295686	T vs C	3	1.34	0.79–2.27	0.28	R	0.0009	86	1.04	0.30
	TT vs CC		1.61	0.59–4.40	0.35	R	0.01	77	1.04	0.30
	CT vs CC		1.38	0.67–2.87	0.38	R	0.002	84	1.04	0.30
	CT + TT vs CC		1.44	0.71–2.95	0.32	R	0.001	85	1.04	0.30
	TT vs CT + CC		1.42	0.54–3.69	0.48	R	0.01	78	0.00	1.00
IL-4 -590C/T rs2243250	T vs C	12	1.22	0.97–1.54	0.09	R	<0.00001	81	0.48	0.63
	TT vs CC		1.55	1.08–2.22	0.02	R	0.01	53	0.75	0.45
	CT vs CC		1.29	1.06–1.56	0.01	F	0.06	42	0.21	0.84

SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity			Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z	p
	CT + TT vs CC		1.44	1.06–1.95	0.02	R	0.01	55	0.21	0.84
	TT vs CT + CC		1.28	1.05–1.55	0.01	R	0.02	53	1.58	0.12
Asians	T vs C	10	1.20	0.91–1.57	0.19	R	<0.00001	84	-	-
	CT + TT vs CC		1.45	0.96–2.19	0.08	R	0.005	62	-	-
	T vs C		1.25	0.92–1.69	0.15	R	<0.00001	84	-	-
Chinese	T vs C		1.25	0.92–1.69	0.15	R	<0.00001	84	-	-
	CT + TT vs CC	9	1.79	1.38–2.33	<0.0001	F	0.38	7	-	-
	T vs C		1.25	0.92–1.69	0.15	R	<0.00001	84	-	-
ADRB2 -46 G /A rs1042713	G vs A	8	1.00	0.52–1.02	0.99	R	<0.00001	85	0.37	0.71
	GG vs AA		1.04	0.63–1.01	0.87	R	<0.00001	82	0.37	.071
	GA vs AA		1.09	0.84–1.42	0.51	R	0.04	52	1.86	0.06
	GA + GG vs AA		1.08	0.78–1.48	0.64	R	0.0009	72	0.62	0.54
	GG vs GA + AA		0.96	0.63–1.46	0.83	R	<0.00001	83	0.87	0.39
Asians	G vs A	4	0.88	0.55–1.41	0.60	R	<0.00001	91	-	-
	GA + GG vs AA		1.03	0.63–1.67	0.91	R	0.0003	81	-	-
ADRB2 -79G/C rs1042713	G vs C	6	1.14	0.88–1.48	0.31	R	0.04	56	0.75	0.45
	GG vs CC		1.19	0.06–1.56	0.46	F	0.63	0	0.75	0.45
	GC vs CC		1.14	0.62–1.42	0.22	F	0.08	48	0.00	1.00
	GC + GG vs CC		1.18	0.87–1.61	0.28	R	0.05	54	0.75	0.45
	GG vs GC + CC		1.09	0.69–1.70	0.72	F	0.71	0	0.38	0.71
Asians	G vs C	3	1.08	0.65–1.80	0.75	R	0.005	81	-	-
	GC + GG vs CC		1.12	0.63–1.98	0.71	R	0.008	79	-	-
ADAM33 F + 1 rs511898	T vs C	5	1.33	0.99–1.79	0.06	R	0.0004	80	-0.24	1.00
	TT vs CC		1.81	0.95–3.44	0.07	R	0.0007	79	-0.24	1.00
	CT vs CC		1.13	0.93–1.36	0.21	F	0.93	0	0.73	0.46
SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model										

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity			Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z	p
	CT + TT vs CC		1.24	1.04–1.48	0.02	F	0.13	44	0.24	0.81
	TT vs TC + CC		1.67	0.94–2.97	0.08	R	0.0007	79	0.24	0.81
Asians	T vs C	4	1.23	0.90–1.67	0.19	R	0.008	75	-	-
	CT + TT vs CC		1.15	0.94–1.40	0.18	F	0.26	25	-	-
ADAM33 V4 rs2787094	G vs C	5	0.99	0.47–2.09	0.99	R	<0.00001	97	-0.24	1.00
	GG vs CC		1.22	0.34–4.32	0.76	R	<0.00001	94	0.24	0.81
	GC vs CC		1.17	0.66–2.08	0.59	R	0.0006	79	0.73	0.46
	GC + GG vs CC		1.02	0.47–2.22	0.96	R	<0.00001	90	1.22	0.22
	CC vs CG + CC		1.15	0.44–3.01	0.78	R	<0.00001	95	0.24	0.81
ADAM33 S2 rs528557	G vs C	4	0.78	0.28–2.11	0.65	R	<0.00001	97	0.34	0.73
	GG vs CC		0.66	0.10–4.60	0.68	R	<0.00001	96	1.02	0.31
	GC vs CC		0.84	0.38–1.83	0.66	R	<0.00001	89	1.70	0.90
	GC + GG vs CC		0.73	0.25–2.18	0.58	R	<0.00001	95	1.02	0.31
	GG vs GC + CC		0.76	0.17–3.47	0.73	R	<0.00001	95	0.34	0.73
Asians	G vs C	3	0.73	0.18–3.00	0.66	R	<0.00001	98	-	-
	GC + GG vs CC		0.67	0.15–3.04	0.60	R	<0.00001	97	-	-
ADAM33 T2 rs2280090	A vs G	4	1.86	1.10–3.15	0.02	R	<0.0001	86	-0.34	1.00
	AA vs GG		4.25	2.27–7.98	<0.00001	F	0.15	43	0.34	0.73
	AG vs GG		1.71	1.03–2.85	0.04	R	0.002	79	-0.34	1.00
	AG + AA vs GG		1.87	1.07–3.27	0.03	R	0.0003	84	-0.34	1.00
	AA vs GA + GG		3.72	1.98–6.98	<0.0001	F	0.27	23	0.34	0.73
Asians	A vs G	3	2.26	1.29–3.94	0.004	R	0.002	85	-	-
	AG + AA vs GG		2.29	1.25–4.17	0.007	R	0.002	83	-	-

SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity			Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z	p
ADAM33 T1 rs2280091	G vs A	4	1.54	0.90–2.65	0.12	R	<0.00001	90	1.70	0.90
	GG vs AA		4.11	2.56–5.90	<0.00001	F	0.03	67	1.02	0.31
	GA vs AA		2.05	1.37–3.08	0.0005	R	0.06	60	0.34	0.73
	GA + GG vs AA		2.12	1.29–3.47	0.003	R	0.007	75	1.02	0.31
	TT vs TC + CC		1.70	0.65–4.45	0.28	R	<0.0001	87	0.34	0.73
Asians	G vs A	3	1.72	0.95–3.14	0.08	R	<0.0001	91	-	-
	GA + GG vs AA		2.92	2.35–3.63	<0.00001	F	0.34	8	-	-
ADAM33 ST + 4 rs44707	C vs A	3	1.57	1.32–1.87	<0.00001	F	0.62	0	0.00	1.00
	CC vs AA		2.19	1.55–3.12	<0.0001	F	0.56	0	1.04	0.30
	AC vs AA		1.59	1.18–2.13	0.002	F	0.16	45	1.04	0.30
	AC + CC vs AA		1.81	1.37–2.39	<0.0001	F	0.37	0	1.04	0.30
	CC vs AC + AA		1.74	1.31–2.30	0.0001	F	0.47	0	0.00	1.00
ORMDL3 rs7216389	T vs C	3	1.81	1.45–2.25	<0.00001	F	0.76	0	0.00	1.00
	TT vs CC		3.35	1.24–7.57	<0.00001	F	0.09	0	0.00	1.00
	CT vs CC		1.98	1.11–3.56	0.02	F	0.94	0	0.00	1.00
	CT + TT vs CC		2.76	1.58–4.82	0.0004	F	0.92	0	0.00	1.00
	TT vs TC + CC		1.89	1.44–2.47	<0.00001	F	0.84	0	0.00	1.00
VDR ApaI rs7975232	C vs A	5	1.31	1.06–1.62	0.01	F	0.12	46	1.22	0.22
	CC vs AA		1.94	1.17–3.24	0.01	F	0.23	31	-0.34	1.00
	AC vs AA		2.18	1.34–3.56	0.002	F	0.78	0	-0.34	1.00
	AC + CC vs AA		1.95	1.26–3.01	0.003	F	0.38	2	0.34	0.73
	CC vs AC + AA		1.36	0.84–2.21	0.21	R	0.06	55	0.73	0.46
Asians	C vs A	3	1.60	1.13–2.27	0.008	F	0.32	12	-	-
SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model										

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity			Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z	p
	AC + CC vs AA		2.10	0.64–6.90	0.22	R	0.10	63	-	-
VDR FokI rs2228570	T vs C	6	1.36	0.99–1.86	0.06	R	0.03	60	0.38	0.71
	TT vs CC		1.85	0.93–3.70	0.08	R	0.04	57	0.75	0.45
	TC vs CC		1.27	0.91–1.76	0.16	F	0.21	30	0.38	0.71
	TC + TT vs CC		1.39	1.02–1.89	0.04	F	0.07	50	0.75	0.45
	TT vs TC + CC		1.50	1.12–2.01	0.006	F	0.17	36	0.00	1.00
Asians	T vs C	3	1.13	0.68–1.89	0.64	R	0.05	67	-	-
	TC + TT vs CC		1.10	0.72–1.70	0.65	F	0.31	13	-	-
VDR BsmI rs1544410	A vs G	5	1.47	1.15–1.88	0.002	F	0.24	27	1.71	0.09
	AA vs GG		1.79	1.03–3.11	0.04	F	0.22	34	0.00	1.00
	AG vs GG		1.91	1.02–3.58	0.04	R	0.08	51	0.24	0.81
	AG + AA vs GG		1.61	1.16–2.25	0.005	F	0.15	41	1.22	0.22
	AA vs AG + GG		1.74	1.05–2.88	0.03	F	0.19	42	0.00	1.00
Asians	A vs G	4	1.81	1.15–2.85	0.01	F	0.20	36	-	-
	AG + AA vs GG		2.26	1.34–3.82	0.002	F	0.22	32	-	-
VDR TaqI rs731236	C vs T	4	0.81	0.50–1.30	0.38	R	0.01	72	1.02	0.31
	CC vs TT		0.90	0.27–2.97	0.18	R	0.008	79	0.00	1.00
	CT vs TT		1.09	0.40–2.97	0.86	R	0.001	81	1.02	0.31
	CT + CC vs TT		0.93	0.37–2.29	0.87	R	0.002	80	1.02	0.31
	CC vs CT + TT		0.63	0.26–1.54	0.31	R	0.01	77	0.00	1.00
CTLA-4 + 49 A/G rs231775	A vs G	3	1.22	0.52–2.88	0.64	R	0.002	84	0.00	1.00
	AA vs GG		1.48	0.30–7.40	0.63	R	0.007	80	0.00	1.00
	AG vs GG		1.28	0.84–1.95	0.24	F	0.20	37	1.04	0.30

SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model

Gene SNPs	Comparison	N	Test of association			Test of heterogeneity		Begg's test	
			OR	95%CI	P	Model	P	I ² /%	z p
	AG + AA vs GG		1.20	0.50–2.89	0.68	R	0.03	71	0.00 1.00
	AA vs AG + GG		1.51	0.40–5.70	0.54	R	0.02	74	0.00 1.00

SNPs: single nucleotide polymorphisms, N: number of studies, OR: odds ratio, 95% CI: 95% confidence interval, R: random-effect model, F: fixed-effect model

IL-13 + 2044G/A polymorphism and pediatric asthma risk

The association between *IL-13* + 2044G/A polymorphism and pediatric asthma risk was evaluated in 5 case-control studies, including 921 cases and 920 controls. The result of meta-analysis shown that the AG and AG + AA genotypes was associated with pediatric asthma risk when compared with GG genotype (AG vs GG: OR = 1.79, 95% CI:1.18–2.72, P = 0.006; GA + AA vs GG: OR = 1.80, 95% CI:1.14–2.28, P = 0.01) in random-effects model. And allele A was associated with increased risk of pediatric asthma (A vs G: OR = 1.52, 95% CI:1.15–2.01, P = 0.004). No association between gene polymorphism and asthma risk was found in homozygous and recessive models. Subgroup analysis showed that a significant increased risk was found in Asian populations under allelic and dominant model(A vs G: OR = 1.93, 95% CI:1.51–2.48, P<0.00001; GA + AA vs GG: OR = 2.56, 95% CI:1.83–3.58, P<0.00001).

IL-4 -590C/T polymorphism and pediatric asthma risk

12 case-control studies including 2532 patients and 2827 controls were investigated. A significant association between *IL-4* -590C/T polymorphism and pediatric asthma risk was shown under the homozygous model (TT vs CC: OR = 1.55, 95% CI:1.08–2.22, P = 0.02), heterozygous model (CT vs CC: OR = 1.29, 95% CI:1.06–1.56, P = 0.01), dominant model (CT + TT vs CC: OR = 1.44, 95% CI:1.06–1.95, P = 0.02) and recessive model (TT vs CT + CC: OR = 1.28, 95% CI:1.05–1.55, P = 0.01). Subgroup analysis showed that significant associations of *IL-4* -590C/T polymorphism with asthma risks among Chinese children in the dominant model (CT + TT vs CC: OR = 1.79, 95% CI:1.38–2.33, P<0.0001). No association was found in Asian populations. Figure 2 showed forest plots of the association between the *IL-4* -590C/T polymorphism and asthma risk. The results of sensitivity analysis found that a study (Dixit 2014) had a great impact on heterogeneity. After omitting this study, the between-study heterogeneity effectively decreased and fixed-effects model was applied: homozygous model (TT vs CC: OR = 1.85, 95% CI:1.44–2.37, P<0.00001, I² = 9%), heterozygous model (CT vs CC: OR = 1.49, 95% CI:1.21–1.85, P = 0.0002, I² = 0%), dominant model (CT + TT vs CC: OR = 1.64, 95% CI:1.34–2.00, P<0.00001, I² = 8%). Other models have not changed significantly. We discovered that there is no directional change in the results after omitting this study, indicating that our results are statistically stable.

ADAM33 F + 1 polymorphism and pediatric asthma risk

We analyzed 1340 cases and 959 controls from five case-control studies. Combined data revealed that the TC + TT genotypes of *ADAM33* F + 1 polymorphism was associated with an increased risk of pediatric asthma (TC + TT vs CC: OR = 1.24, 95% CI:1.04–1.48, P = 0.02) and revealed no statistically significant link between *ADAM33* F + 1 polymorphism and the risk of childhood asthma in the allelic model(T vs C: OR = 1.33, 95% CI:0.99–1.79, P = 0.06), homozygous model(TT vs CC: OR = 1.81, 95% CI:0.95–3.44, P = 0.07), heterozygous model (TC vs CC: OR = 1.13, 95% CI:0.93–1.36, P = 0.21)and recessive model (TT vs TC + CC: OR = 1.67, 95% CI:0.94–2.97, P = 0.08). No association was found between *ADAM33* F + 1 polymorphism and pediatric asthma risk among Asian populations. Sensitivity analysis showed these results are instable. F + 1 was significantly associated with childhood asthma after omitting one study (Qu2011)³⁴: allelic model (T vs C: OR = 1.48, 95% CI:1.14–1.92, P = 0.003), homozygous model (TT vs CC: OR = 2.34, 95% CI:1.40–3.92, P = 0.001), dominant model (TC + TT vs CC: OR = 1.43, 95% CI: 1.13–1.80, P = 0.003), recessive model (TT vs TC + CC: OR = 2.31, 95% CI:1.74–3.07, P<0.00001).

ADAM33 T2 polymorphism and pediatric asthma risk

Four studies containing 928 cases and 967 controls were synthesized. The result indicated that an increased risk of childhood asthma was observed in all the four models of *ADAM33* T2 polymorphism: allelic model (A vs G: OR = 1.86, 95% CI:1.10–3.15, P = 0.02), homozygous model (AA vs GG: OR = 4.25, 95% CI:2.27–7.98, P<0.00001), heterozygous model (AG vs GG: OR = 1.71, 95% CI:1.03–2.85, P = 0.04), dominant model (AG + AA vs GG: OR = 1.87, 95% CI:1.07–3.27, P = 0.03), recessive model (AA vs GA + GG: OR = 3.72, 95% CI:1.98–6.98, P<0.0001). Subgroup analysis showed that the allele A and AG + AA genotype was associated with increased asthma risk in Asian populations (A vs G: OR = 2.26, 95% CI:1.29–3.94, P = 0.004; AG + AA vs GG: OR = 2.29, 95% CI:1.25–4.17, P = 0.007).

ADAM33 T1 polymorphism and pediatric asthma risk

4 case-control studies included 938 cases 928 controls. Compared with AA genotype, GG, GA and GA + GG genotype increased the susceptibility to asthma (GG vs AA: OR = 4.11, 95% CI:2.56–5.90, $P < 0.00001$; GA vs AA: OR = 2.05, 95% CI:1.37–3.08, $P = 0.0005$; GA + GG vs AA: OR = 2.12, 95% CI:1.29–3.47, $P = 0.003$). No association between gene polymorphism and asthma risk was found in allelic and recessive models. The results of subgroup analysis showed that GA + GG genotype may increase the risk of childhood asthma in Asian populations (GA + GG vs AA : OR = 2.92, 95% CI: 2.35–3.63, $P < 0.00001$).

ADAM33 ST + 4 polymorphism and pediatric asthma risk

When three studies containing 716 cases and 435 controls on *ADAM33* ST + 4 polymorphism were combined, the analysis showed that the correlation between *ADAM33* ST + 4 polymorphism and pediatric asthma risk was statistically significant in all genetic models under fixed-effects model: allelic model (G vs A: OR = 1.57, 95% CI:1.32–1.87, $P < 0.00001$), homozygous model (CC vs AA: OR = 2.19, 95% CI:1.55–3.12, $P < 0.0001$), heterozygous model (AC vs AA: OR = 1.59, 95% CI:1.18–2.13, $P = 0.002$), dominant model (AC + CC vs AA: OR = 1.81, 95% CI:1.37–2.39, $P < 0.0001$), recessive model (CC vs AC + AA: OR = 1.74, 95% CI:1.31–2.30, $P = 0.0001$).

ORMDL3 rs7216389 polymorphism and pediatric asthma risk

We synthesized three studies including 448 cases and 478 controls. The results revealed that ORMDL3 rs7216389 polymorphism was associated with a high risk of childhood asthma in all four genetic model: allelic model (T vs C: OR = 1.81, 95% CI: 1.45–2.25, $P < 0.00001$), homozygous model (TT vs CC: OR = 3.35, 95% CI: 1.24–7.57, $P < 0.00001$), heterozygous model (TC vs CC: OR = 1.98, 95% CI: 1.11–3.56, $P = 0.02$), dominant model (TC + TT vs CC: OR = 2.76, 95% CI:1.58–4.82, $P = 0.0004$), recessive model (TT vs TC + CC: OR = 1.89, 95% CI: 1.44–2.47, $P < 0.00001$).

VDR ApaI polymorphism and pediatric asthma risk

Five studies included 426 cases and 476 controls. Our analysis suggested that VDR ApaI polymorphism were associated with high pediatric risk under allelic (C vs A: OR = 1.31, 95% CI:1.06–1.62, $P = 0.01$), homozygous (CC vs AA: OR = 1.94, 95% CI:1.17–3.24, $P = 0.01$), heterozygous (AC T vs AA: OR = 2.18, 95% CI:1.34–3.56, $P = 0.002$) and dominant model (AC + CC vs AA: OR = 1.95, 95% CI:1.26–3.01, $P = 0.003$). Subgroup analysis showed that the allele C was associated with increased asthma risk in Asians population (C vs A: OR = 1.60, 95% CI:1.13–2.27, $P = 0.008$).

VDR FokI polymorphism and pediatric asthma risk

Six studies included 503 cases and 465 controls. Results revealed that VDR FokI polymorphism was associated with increased risk of childhood asthma in dominant model (TC + TT vs CC: OR = 1.39, 95% CI:1.02–1.89, $P = 0.04$) and recessive model (TT vs TC + CC: OR = 1.50, 95% CI:1.12–2.01, $P = 0.006$) under fixed-effects model. No association was found in other models. Subgroup analysis did not find a significant relationship in Asians.

VDR BsmI polymorphism and pediatric asthma risk

Five studies included 430 cases and 496 controls. Our result found VDR BsmI polymorphism were associated with increased the risk of asthma under four genetic comparison models: allelic model (A vs G: OR = 1.47, 95% CI:1.15–1.88, $P = 0.002$), homozygous model (AA vs GG: OR = 1.79, 95% CI:1.03–3.11, $P = 0.04$), heterozygous model (AG vs GG: OR = 1.91, 95% CI:1.02–3.58, $P = 0.04$), dominant model (AG + AA vs GG: OR = 1.74, 95% CI:1.05–2.88, $P = 0.03$) and recessive model (AA vs AG + GG: OR = 1.61, 95% CI:1.16–2.25, $P = 0.005$). Subgroup analysis showed VDR BsmI polymorphism was related with childhood asthma in Asian populations (A vs G: OR = 1.81, 95% CI:1.15–2.85, $P = 0.01$; AG + AA vs GG: OR = 2.26, 95% CI:1.34–3.82, $P = 0.002$).

No association between other 8 gene polymorphism (IL-13 -1112C/T, IL-13 + 1923 C/T, ADRB2 -46 G /A, ADRB2 -79G/C, ADAM33 V4, ADAM33 S2, CTLA-4 + 49 A /G, VDR TaqI) and susceptibility to pediatric asthma was found in total population and in Asians.

Sensitivity analysis and publication bias

We applied sensitivity analysis to assess the impact of each study on overall results. Sensitivity analysis showed that the results of *IL-13* -1112C/T, *VDR* TaqI, *ADAM33* S2 and *ADAM33* F + 1 polymorphism were unstable. Sensitivity analysis of other polymorphisms showed that that the pooled ORs were not significantly changed. Publication bias was estimated by funnel plot, Begg's test and Egger's test. The results of Begg's test were summarized in Table 2. (Begg's funnel plots can be seen in Additional File 1.) Except for the *IL-13* + 2044 C/T polymorphism (under allelic model), no evidence of publication bias was observed.

Discussion

It is well-known that single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among people, which are closely associated with susceptibility to individual disease⁵⁵. Many studies on the association between SNP and childhood asthma have shown mixed results. Meta-analysis is a combination of comparable studies that increase the sample size to get more convincing results. The aim of this study was to analyze the strength of the association between partial SNPs and pediatric asthma. We finally identified 18 polymorphisms in 7 genes. According to the characteristics of the included studies, we performed subgroup analysis of Asians. We believe this is the first comprehensive genetic meta-analysis for pediatric asthma.

IL-13 and *IL-4*, with various biological activities, are associated with the inflammatory response and fibrosis in T helper 2 (Th2) inflammation and play an important role in the development of asthma⁵⁶. Biologics targeting *IL-4* and *IL-13* are expected to be a promising treatment for asthma in the future⁵⁷. Our results demonstrated that *IL-13*+2044G/A and *IL-4*-590C/T polymorphism were associated with asthma risk in total populations and Asians, *IL-13*-1112C/T and *IL-13*+1923C/T polymorphism were not associated with the risk of childhood asthma in any of the models. These results are partially consistent with the previous meta-analyses: Liu et al.⁵⁸ and Mei et al.⁵⁹ found that *IL-13*+2044A/G polymorphism was significantly associated with asthma risk in Asian children; Zhang et al.⁶⁰ found that a strong association between the *IL-4*-590 C/ T polymorphism and the risk of childhood asthma; a meta-analysis showed that *IL-4*-590 C/ T polymorphism was associated with asthma risk among Chinese children. In line with these findings, we presume *IL-13*+2044 A/G and *IL-4*-590 C/ T polymorphism maybe risk factors in pediatric asthma. However, some studies have shown that *IL-13*-1112C/T and *IL-13*+1923C/T variant were correlated with increased risk of asthma in children^{58,59,61}, which is different from our results. The reasons may be the following: a significantly increased risk between *IL-13*-1112C/T and asthma risk was observed by Liu et al.⁵⁸ in overall populations, but not in Asians. Probably because of the different retrieval methods and inclusion criteria, most of the population we included were Asian. In addition, the instability of the results may also be responsible for the differences. For *IL-13*+1923C/T polymorphism, inconsistent results may be due to the small number of studies we included. More data are required to investigate these associations.

ADAM33 gene has been identified as a susceptibility gene for asthma by positional cloning. This gene, localized on chromosome 20p13, is expressed in human lung fibroblasts and bronchial smooth muscle and plays an important role in airway remodeling and airway hyperresponsiveness in asthma⁶². Our results showed that ST + 4, T1, T2 and F + 1 polymorphisms of *ADAM33* gene were significantly associated with asthma risks among the overall children and Asians, which mostly confirm previous studies. A meta-analysis performed by Li et al.⁶³ showed that F + 1, ST + 4 and T2 polymorphisms of *ADAM33* gene were associated with pediatric asthma susceptibility and S2, V4 and polymorphisms were not associated with childhood asthma risk. Deng et al.⁶⁴ found that T1 polymorphism was associated with asthma risks among Asian children. Therefore, *ADAM33* gene could be proposed as childhood asthma susceptible gene.

Moffatt et al.⁶⁵ identified *ORMDL3* located at 17q21.1 as a candidate gene for asthma and indicated SNP rs7216389 was the most correlated with asthma. The sequence around rs7216389 contains regions that are homologous to pro-inflammatory transcription factors. Our study and other studies^{66–68} have shown a significant association between rs7216389 and susceptibility to childhood asthma.

VDRs are associated with the occurrence and development of asthma. *VDR* is an intranuclear macromolecule that mediates 1,25 (OH) D to exert biological effects. Serum 25 (OH) D level is negatively correlated with asthma, and vitamin D level has a significant relationship with lung function test outcomes in children with asthma⁶⁹. In the past few years, research on the correlation between *VDR* and asthma has focused on four SNPs: Apal, FokI, BsmI and TaqI. Our meta-analysis showed that Apal, FokI, and BsmI polymorphisms contribute to childhood asthma susceptibility, while there was no evidence of the association between TaqI SNP and pediatric asthma risk, which confirms the previous research results⁷⁰. And we found that Apal and BsmI polymorphisms may be associated with asthma in Asian populations.

The *ADRB2* gene is abundantly expressed on bronchial smooth muscle and can activate β -adrenergic receptors, thereby regulating the constriction function of bronchial smooth muscle. The amino acid sequence of *ADRB2* gene can affect the function of β -adrenergic receptor⁷¹. *CTLA-4* can improve airway hyperresponsiveness and plays an important role in the pathogenesis of asthma⁷². Our results and Guo et al.⁷³ found -46 G / A and -79G/C polymorphisms of *ADRB2* gene were not associated with a risk of childhood asthma. However, some studies^{74,75} indicated that -79G/C polymorphism was associated with a reduced risk for the development of pediatric asthma. Some meta-analysis^{76,77} found that *CTLA-4*+49 A/G polymorphism might be a risk factor for asthma susceptibility, which contradicts our results. Further studies on larger samples are required to produce more accurate outcomes.

Finally, several limitations to the present study should be considered. First, we searched the literature for the past ten years, the numbers of published studies were insufficient for a comprehensive analysis, therefore, we only performed a subgroup analysis of Asian populations. Second, due to the lack of original individual data in the included literature, the unadjusted OR value was used for the combined analysis in this study, which may reduce the accuracy of the results. Third, certain studies have shown that multiple SNPs may act together to increase the risk of asthma. The association between SNP and asthma was influenced by region, ethnicity, age, gender, etc. The effect of individual genes on asthma is small, and many complex causes such as gene-gene interactions and gene-environment interactions contribute to asthma, which need more studies to determine.

Conclusion

In summary, this meta-analysis suggested that ten gene polymorphisms (*IL-13* + 2044G/A, *IL-4* -590C/T, *ADAM33* F + 1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST + 4, *ORMDL3* rs7216389, *VDR* Apa $\text{\AA}$, *VDR* Fok $\text{\AA}$, *VDR* Bsm $\text{\AA}$) might be risk factors for pediatric asthma susceptibility. Moreover, *IL-13* + 2044G/A, *ADAM33* T2, *ADAM33* T1, *VDR* Apa $\text{\AA}$, *VDR* Bsm $\text{\AA}$ polymorphisms may cause an increased risk of asthma among Asian populations. *IL-4* -590C/T polymorphisms may be related to asthma risk in Chinese children. These results have reference significance for the exploration of pathologic mechanism and further treatment of childhood asthma. However, due to some limitations, studies with larger samples are needed for further study in detail.

Abbreviations

COPD: Chronic obstructive pulmonary disease; GWAS: Genome-wide association study; HWE: Hardy-Weinberg equilibrium; SNP: Single nucleotide polymorphism; ADAM33: A Disintegrin and Metalloprotease33; IL: Interleukin; ORMDL3: Orosomucoid 1-like 3; VDR: Vitamin D receptor; ADRB2: β -2 adrenergic receptor; CTLA-4: Cytotoxic T lymphocyte associated antigen-4; CI: Confidence interval; MeSH: Medical Subject Heading; OR: Odds ratio

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The databases which we collected Literature include PubMed, Embase, Web of science and Chinese database (China National Knowledge Infrastructure, WanFang and Weipu) between January 2010 and January 2020.

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Competing interests

All authors declare that they have no competing interests.

Author contributions

RZ and DH conceived of the project and designed the study. RZ and DH wrote the manuscript. RZ and SZL participated in selecting study and extracting data. DH, KJS and ZGC take part in Manuscript Revise. KJS was in charge of quality control. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow chart of the selection process.

Figure 2

Forest plots of the association between the IL-4 -590C/T polymorphism and asthma risk

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