Interleukin-4 gene polymorphism (C33T) and the risk of the asthma: A meta-analysis based on 24 studies

CURRENT STATUS: UNDER REVIEW

BMC Medical Genetics BMC Series

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DOI:
10.21203/rs.2.20557/v1

SUBJECT AREAS
Medical Genetics

KEYWORDS
IL-4 C33T polymorphism, bronchial asthma, meta-analysis, association

Abstract

Background

Previous studies evaluate an association of IL-4 C33T polymorphism and risk of bronchial asthma but failed to establish a consistent conclusive association between the two. In the present meta-analysis, we intend to define a more reliable estimate of the association in the presence of filling published literature.

Methods

An exhaustive search in web of science, Scopus, and PubMed databases was performed to identify all relevant publications before November 2019, and 24 studies with 6587 cases and 8408 controls were included in final analysis. The association between polymorphism and risk of asthma were measured by Odd ratios (ORs) and 95% confidence intervals (CIs). Moreover, Cochran Q and the I2 statistics were used to evaluated the degree of heterogeneity between studies

Results

In the overall study populations, the result illustrated that IL-4 C33T polymorphism was a risk factor in the pathogenesis of asthma. In the subgroup analysis by age, a significant association between IL-4 SNP (C33T) and risk of asthma in different age groups was identified in allelic model, which highlighted the predisposing role of the T allele for the asthma risk in all three age groups. In the Asian population, there was a significant association between IL-4 SNP (C33T) and risk of asthma under recessive and allelic models. Finally, there was a significant association between IL-4 SNP (C33T) and asthma risk in Caucasian under recessive model and allelic model.

Conclusions

This study suggests that IL-4 C33T single nucleotide polymorphism potentially acts as a risk factor for asthma in different ethnicities and age groups.

Background

Asthma is a chronic, complex respiratory disorder in which allergen-triggered inflammatory reactions in the airways contribute to the development of symptoms, including breathlessness, cough, wheezing, and dyspnea [1]. It has been estimated that asthma affect about 300 million people in the

world [2]. Prognostic markers to detect high-risk individuals are urgently required for early identification and preventive attention. In the scientific community, genetic vulnerability to asthma is one of the main research interests [3]. In the recent decade, many studies have been focused to elucidate the susceptibility genes of asthma and several single nucleotide polymorphisms (SNPs) in these genes have been described to be related with asthma risk in different populations[4, 5]. Among different genes, interleukin 4 (IL-4) gene has been comprehensively investigated [6, 7]. IL-4 plays a major function in isotype class switching of B cells to IgE production, type 2 immune responses, and it is involved in recruitment of mast cell [8]. It has thus been proposed that IL-4 may have an imperative role in the development and persistent of asthma [8]. IL-4 gene is located on long arm of chromosome 5 (5q31), a region that has been associated with asthma or related disorders such as bronchial hyper responsiveness (BHR) and atopy [9]. The IL-4 C33T single nucleotide polymorphism (rs2070874) which is located on the untranslated region (UTR) has been represented to be linked with elevated serum IgE levels and risk of asthma [10–12]. There are several studies in which association between IL-4 C33T polymorphism and asthma risk have been evaluated [6, 7, 10–31]. Nevertheless, this association remains inconsistent and inconclusive in several studies. Probably, this could be because of the small samples size examined in these studies and the small effect size of the polymorphism that failed to provide sufficient statistical power to identify statically significant associations. Accordingly, we conducted a meta-analysis to conclude a more exact estimation of the relation between the IL-4 -33C/T polymorphism and risk of asthma.

Methods:

The current meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[32].

Search strategy:

An exhaustive search in web of science, Scopus, and PubMed databases was performed to identify all publications evaluate the association between IL-4 C33T polymorphism and asthma risk from inception through November 2019. We applied (“asthma” [Mesh] OR “asthmatic”) AND (“interleukin-4” OR “IL-4” OR “interleukin 4”) AND (“single nucleotide polymorphism” OR “SNP” OR

“polymorphisms” OR “mutation” OR “variation”), as main key words in our search. Besides, references of eligible studies were screened for additional relevant papers.

Inclusion and exclusion criteria:

Primary search strategy generates 1873 studies that exported to Endnote X8. The duplicate studies were removed and title and abstract of remain studies were reviewed by two investigators. Full-text verification was performed if we could not categorize studies based on title and abstract. Eventually, studies considered eligible if met the following criteria: 1) publications with distinct case and control group that evaluate the association between IL-4 C33T polymorphism and the risk of asthma as the main outcome; 2) publications with sufficient data to extract or calculate odds ratios (ORs) and 95% confidence intervals; 3) publications that report genotype or allele distributions of case and healthy individuals. The duplicates, reviews, book chapters, and meta-analysis were excluded. The application of these criteria results in 24 qualified studies for the meta-analysis.

Data extraction and quality assessment:

Two of our authors independently and according to an extraction checklist extracted the following data: the first author, journal and year of publication, country of origin, ethnicity, number of subjects in the case and the control groups for each gender, mean or range of age, genotyping method, genotype counts in the case and the control group. The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) criteria[33]. Studies with scores 0–3, 4–6 or 7–9 were low, moderate or high-quality, respectively.

Statistical analysis:

Deviation from Hardy–Weinberg equilibrium (HWE) for genotype frequency was evaluated by chi-square test in the control group. The association between polymorphism and risk of asthma were measured by Odd ratios (ORs) and 95% confidence intervals (CIs). Moreover, Cochran Q and the I2 statistics were used to evaluated the degree of heterogeneity between studies (I2 = (Q–df)/Q _ 100%; I2 < 25%, no heterogeneity; I2 = 25–50%, moderate heterogeneity; I2 = 50–75%, large heterogeneity, I2 > 75%, extreme heterogeneity) [34]. In the presence of heterogeneity, model is considered as a heterogeneous one and a random effect model (REM) should be used. Otherwise, fixed effect

model(FEM) should be applied [35]. The stability of the results was evaluated by sensitivity analysis. Furthermore,

publication bias was investigated, using Begg's and Egger's tests along with visual examination of the funnel plot (p value < 0.05 considered statistically significant) [36]. All data analysis was accomplished using SPSS (version 23; Chicago, IL, USA) and Stata (version 14; Stata Corporation, College Station, TX) software.

Results:

Study characteristics

Regarding to aforementioned keywords total of 1873 studies were initially retrieved. Of these studies, 219 publications were duplicate, 1496 and 134 publications excluded by title & abstract and full text examination, respectively. Finally, 24 studies qualified for quantitative analysis Fig. 1. The eligible studies were published from 2000 to 2016 and had an overall good methodological quality with NOS scores ranging from 5 to 8. Different genotyping method were used by included studies. Tables 1 and 2 summarized the characteristics and genotype frequency of the included studies.

Table 1

Characteristics of studies included in meta-analysis of overall asthma.

Study author	Year	Country	Ethnicity 1	Ethnicity 2	Sex cases/controls	Total cases/controls	Age case/control	Genotyping method	Quality score
Suzuki et al.	2000	Japan	Asian	Caucasian	M = 50/60 F = 100/150	120 / 120	Adult	PCR-RFLP	6
Beghe et al.	2003	UK	European	Caucasian	M = 88/99 F = 93/89	187 / 182	Adult	PCR-RFLP	7
Basehore et al.(i)	2004	USA	American	American - African	M = 93/140 F = 98/147	233 / 245	Adult	PCR	7
Basehore et al.(ii)	2004	USA	American	American - African	M = 77/91 F = 121/148	168 / 269	Adult	PCR	6
Basehore et al.(iii)	2004	USA	American	American - African	M = 54/62 F = 41/89	116 / 130	Adult	PCR	6
Park et al.	2004	Korea	Asian	Caucasian	M = 248/302 F = 85/86	532 / 170	Mixed	SnaP shot	8
Donfack et al.(i)	2005	USA	American	American - African	M = NR F = NR	126 / 205	Mixed	LAS	6
Donfack et al.(ii)	2005	USA	American	American - African	M = NR F = NR	205 / 183	Mixed	LAS	6
Garcia et al.	2005	Spain	European	Caucasian	M = NR F = NR	133 / 79	Mixed	TaqMan	6
Battle et al.	2007	USA	American	American - African	M = 105/156 F = 67/109	261 / 176	Mixed	PCR-RFLP	6
Amirzargar et al.	2009	Iran	Asian	Caucasian	M = NR F = NR	59 / 139	Mixed	PCR-SSP	5

al et al.				n	F = NR				
Jiang et al.	2009	China	Asian	Caucasian	M = NR F = NR	24 / 24	Adult	PCR-RFLP	5
Daley et al.	2009	Australia	Australian	Caucasian	M = NR F = NR	643 / 751	Mixed	Illumina Bead array system	8
Haller et al.	2009	USA	American	American - African	M = NR F = NR	72 / 70	Adult	PCR-RFLP	6
Wang et al.	2009	Taiwan	Asian	Caucasian	M = 299/147 F = 245/265	446 / 510	Children	TaqMan	7
Berce et al.	2010	Slovenia	European	Caucasian	M = NR F = NR	106 / 89	Children	PCR-RFLP	6
Undarma a et al.(i)	2010	Japna	Asian	Caucasian	M = NR F = NR	324 / 336	Children	TaqMan-ASA	7
Undarma a et al.(ii)	2010	Japna	Asian	Caucasian	M = NR F = NR	367 / 676	Adult	TaqMan-ASA	8
Wu et al.	2010	China	Asian	Caucasian	M = 138/114 F = 118/109	252 / 227	Children	PCR-RFLP	7
Michel et al.	2010	Germany	European	Caucasian	M = NR F = NR	703 / 658	Children	Illumina Sentrix Bead chip	8
Huang et al.	2011	China	Asian	Caucasian	M = 51/49 F = 70/52	100 / 122	Children	PCR-RFLP	6
Yang et al.	2011	China	Asian	Caucasian	M = 101/101 F = 155/50	202 / 205	Adult	MALDI-TOF	6
Chen et al.	2011	China	Asian	Caucasian	M = NR F = NR	202 / 191	Children	MALDI-TOF	7
Micheal et al.	2013	Pakistan	Asian	Caucasian	M = NR F = NR	108 / 120	Mixed	PCR-RFLP	6
Miyake et al.	2013	Japan	Asian	Caucasian	M = 0/89 F = 0/1281	89 / 1281	Adult	TaqMan	6
Davoodi et al.	2013	India	Asian	Caucasian	M = 45/55 F = 21/29	100 / 50	Adult	Mass Array	5
Wang et al.	2015	China	Asian	Caucasian	M = NR F = NR	392 / 849	Children	Mass Array	8
Li et al.	2016	China	Asian	Caucasian	M = 134/183 F = 151/200	317 / 351	Children	PCR-RFLP	7
NR, not reported; M, male; F, female									

Table 2

Distribution of genotype and allele among asthma patients and controls.

Study author	Asthma cases					Healthy control					P-HWE	MAF
	CC	CT	TT	C	T	CC	CT	TT	C	T		
Suzuki et al.	11	56	53	78	162	10	59	51	79	161	0/21	0/67
Beghe et al.	140	41	6	321	53	132	48	2	312	52	0/29	0/142
Baseh ore et al.(i)	153	72	8	378	88	185	56	4	426	64	0/91	0/13
Baseh ore et al.(ii)	51	83	34	185	151	87	132	50	306	232	0/99	0/431
Baseh ore et al.(iii)	48	53	15	149	83	60	57	13	177	83	0/92	0/319
Park et al.	19	164	349	202	862	7	57	106	71	269	0/84	0/791

Donfack et al. (i)	83	37	6	203	49	150	50	5	350	60	0/73	0/146
Donfack et al. (ii)	68	107	30	243	167	70	86	27	226	140	0/94	0/382
Garcia et al.	93	39	1	225	41	64	15	0	143	15	0/35	0/094
Battle et al.	85	128	48	298	224	57	87	32	201	151	0/9	0/428
Amirzargar et al.	2	56	1	60	58	61	78	0	200	78	< 0.001	0/28
Jiang et al.	0	9	15	9	39	2	10	12	14	34	0/96	0/708
Daley et al.	481	150	12	1112	174	555	181	15	1291	211	0/95	0/14
Haller et al.	21	36	15	78	66	27	33	10	87	53	0/98	0/378
Wang et al.	22	147	277	191	701	16	186	308	218	802	0/05	0/786
Berce et al.	67	31	8	165	47	51	35	3	137	41	0/3	0/23
Undarmaa et al.(i)	27	142	155	196	452	37	144	155	218	454	0/68	0/675
Undarmaa et al.(ii)	28	154	185	210	524	64	286	326	414	938	0/91	0/693
Wu et al.	6	83	163	95	409	11	87	129	109	345	0/44	0/759
Michel et al.	458	210	35	1126	280	474	173	11	1121	195	0/28	0/148
Huang et al.	1	23	76	25	175	3	49	70	55	189	0/09	0/774
Yang et al.	14	56	132	84	320	7	67	131	81	329	0/65	0/802
Chen et al.	6	72	124	84	320	6	62	123	74	308	0/58	0/806
Michael et al.	77	31	0	185	31	93	27	0	213	27	0/16	0/112
Miyake et al.	12	33	44	57	121	160	604	517	924	1638	0/42	0/639
Davoodi et al.	65	31	4	161	39	36	14	0	86	14	0/24	0/14
Wang et al.	49	176	167	274	510	102	410	337	614	1084	0/18	0/638
Li et al.	147	170	0	464	170	170	181	0	521	181	< 0.001	0/257

P-HWE, p-value for Hardy–Weinberg equilibrium; MAF, minor allele frequency of control group

Meta-analysis of IL-4 SNP (C33T) and the risk of asthma

Twenty-eight studies with 6587 cases and 8408 controls were included in final analysis of overall population. Among these studies, 15 publications were carried out in Asian countries, 5 publications were in American countries and 4 publications were in Europe. Our results showed that IL-4 SNP (C33T) increase risk of asthma across all genotype models including dominant model (OR = 1.15, 95% CI = 1.04–1.26, P = ≤ 0.001, FEM), recessive model (OR = 1.16, 95% CI = 1.06–1.28, P = ≤ 0.001, FEM), allelic model (OR = 1.14, 95% CI = 1.07–1.21, P = ≤ 0.001, FEM), CC vs. TT model (OR = 1.21, 95% CI

= 1.02–1.43, P = 0.02, FEM) and CT vs. TT model (OR = 1.10, 95% CI = 1-1.22, P = 0.05, FEM) Fig. 2. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in Table 3.

Table 3

Main results of pooled ORs in meta-analysis of IL-4 (C33T) gene polymorphisms.

Subgroup	Sample size		Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
	Genetic model	Case/Control	OR	95% CI (p-value)	I^2 (%)	P	z	P	t	P
Overall	Dominant model	6587 / 8404	1.15	1.04–1.26 (≤ 0.001)	20.9	0.16	0.77	0.44	0.90	0.37
	Recessive model	6587 / 8404	1.16	1.06–1.28 ((≤ 0.001)	0	0.56	2.68	0.001	2.88	0.001
	Allelic model	6587 / 8404	1.14	1.07–1.21 (≤ 0.001)	27.8	0.08	2.53	0.01	2.39	0.02
	CC vs. TT	6587 / 8404	1.21	1.02–1.43 (0.02)	0	0.58	1.78	0.07	1.57	0.13
	CT vs. TT	6587 / 8404	1.10	1–1.22 (0.05)	20.5	0.17	0.23	0.81	0.56	0.58
Age groups										
Adults	Dominant model	1678 / 3252	1.16	0.97–1.40 (0.10)	0	0.54	-0.98	0.32	-1.43	0.19
	Recessive model	1678 / 3252	1.17	0.99–1.39 (0.06)	0	0.93	2.41	0.01	3.57	0.007
	Allelic model	1678 / 3252	1.14	1.02–1.26 (0.02)	0	0.75	1.01	0.31	1.44	0.18
	CC vs. TT	1678 / 3252	1.22	0.93–1.61 (0.15)	0	0.72	0.83	0.40	0.64	0.54
	CT vs. TT	1678 / 3252	1.09	0.90–1.32 (0.91)	0.2	0.43	-1.16	0.24	-1.72	0.12
Mixed	Dominant model	2067 / 1823	1.14	0.96–1.34 (0.13)	55.8	0.02	2.23	0.02	3.47	0.01
	Recessive model	2067 / 1823	1.08	0.84–1.40 (0.53)	0	0.89	-0.49	0.62	0.47	0.67
	Allelic model	2067 / 1823	1.14	1.01–1.29 (0.03)	56.9	0.02	2.72	0.007	3.11	0.02
	CC vs. TT	2067 / 1823	1.10	0.77–1.57 (0.60)	0	0.88	1.47	0.14	2.01	0.13
	CT vs. TT	2067 / 1823	1.13	0.95–1.35 (0.15)	53.7	0.03	2.47	0.01	3.38	0.01
Children	Dominant model	2842 / 3333	1.15	0.99–1.34 (0.07)	12.4	0.33	-0.42	0.67	-0.48	0.64

	Recessive model	2842 / 3333	1.18	1.03–1.35 (0.01)	54	0.03	1.24	0.21	2.34	0.05
	Allelic model	2842 / 3333	1.13	1.04–1.24 (≤ 0.001)	44.6	0.07	0.42	0.67	0.47	0.65
	CC vs. TT	2842 / 3333	1.27	0.97–1.65 (0.08)	42.3	0.09	0.99	0.32	0.97	0.36
	CT vs. TT	2842 / 3333	1.08	0.92–1.26 (0.33)	4.5	0.39	-0.42	0.67	-0.64	0.54
Ethnicity1										
Asia	Dominant model	3634 / 5371	1.10	0.93–1.130 (0.25)	29.3	0.13	0.81	0.41	1.44	0.17
	Recessive model	3634 / 5371	1.14	1.02–1.26 (0.01)	0	0.56	0.85	0.39	1.24	0.24
	Allelic model	3634 / 5371	1.12	1.03–1.21 (≤ 0.001)	34.9	0.08	2.31	0.02	2.70	0.01
	CC vs. TT	3634 / 5371	1.08	0.87–1.33 (0.49)	0	0.77	0	1	0.09	0.93
	CT vs. TT	3634 / 5371	1.02	0.89–1.18 (0.76)	29.6	0.12	0.45	0.65	0.93	0.36
Europe	Dominant model	1129 / 1008	1.23	1.01–1.50 (0.03)	48.3	0.12	-0.68	0.49	-0.64	0.58
	Recessive model	1129 / 1008	2.94	1.54–5.62 (≤ 0.001)	0	0.95	-0.52	0.60	-0.85	0.55
	Allelic model	1129 / 1008	1.30	1.10–1.54 (≤ 0.001)	31.2	0.22	0	1	-0.68	0.56
	CC vs. TT	1129 / 1008	3	1.56–5.76 (≤ 0.001)	0	0.87	-0.52	0.60	-1.20	0.44
	CT vs. TT	1129 / 1008	1.13	0.92–1.38 (0.24)	52.8	0.09	-0.68	0.49	-0.59	0.61
America	Dominant model	1181 / 1278	1.26	1.05–1.51(≤ 0.001)	0	0.76	0.45	0.65	0.54	0.61
	Recessive model	1181 / 1278	1.16	0.88–1.52 (0.29)	0	0.89	2.55	0.01	6.60	0.06
	Allelic model	1181 / 1278	1.17	1.03–1.33 (0.01)	0	0.55	1.65	0.09	2.71	0.04
	CC vs. TT	1181 / 1278	1.26	0.93–1.71 (0.14)	0	0.84	2.25	0.02	3.17	0.05
	CT vs. TT	1181 / 1278	1.23	1.02–1.49 (0.03)	0	0.85	0.45	0.65	0.18	0.86
Ethnicity 2										
Caucasian	Dominant model	5406 / 7130	1.11	0.99–1.24 (0.07)	32.6	0.08	0.78	0.43	0.69	0.50
	Recessive model	5406 / 7130	1.17	1.05–1.29 (≤ 0.001)	16.6	0.26	1.98	0.04	2.44	0.02
	Allelic model	5406 / 7130	1.13	1.05–1.21 (≤ 0.001)	37.9	0.04	1.87	0.06	1.79	0.08
	CC vs. TT	5406 / 7130	1.19	0.97–1.46	13.4	0.30	1.14	0.25	0.72	0.48

		[illegible]		[illegible] (0.09)						
	CT vs. TT	5406 / 7130	1.06	0.94–1.19 (0.35)	32.8	0.07	-0.68	0.49	-0.59	0.61
African-American	Dominant model	1181 / 1278	1.26	1.05–1.51 (0.01)	0	0.76	0.45	0.65	0.54	0.61
	Recessive model	1181 / 1278	1.16	0.88–1.52 (0.29)	0	0.89	2.55	0.01	6.60	0.06
	Allelic model	1181 / 1278	1.17	1.03–1.33 (0.01)	0	0.55	1.65	0.09	2.71	0.04
	CC vs. TT	1181 / 1278	1.26	0.93–1.71 (0.14)	0	0.84	2.25	0.02	3.17	0.05
	CT vs. TT	1181 / 1278	1.23	1.02–1.49 (0.03)	0	0.85	0.45	0.65	0.18	0.86

Subgroup analysis

We categorize studies into different subgroups on the basis of age, continent and ethnicity. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in Table 3.

Subgroup analysis by age

In this group, we stratified eligible articles into three groups including: adult (8 articles), children (7 articles) and mixed (cover both ranges; 9 articles). Overall, the results rejected significant association between IL-4 SNP (C33T) and risk of asthma in different age group except for allelic model which highlighted the predisposing role of the T allele for the asthma risk in all three age groups.

Subgroup analysis by continent

Our included studies performed in Asia (15 articles), Europe (4 articles), America (4 articles), and Oceania (1 article). Since there was only one study for Oceania we exclude it. The final results revealed strong significant association between IL-4 SNP (C33T) and asthma risk in European population. Moreover, unlike Asian population there was a significant association between IL-4 SNP (C33T) and risk of asthma in American population under dominant model (OR = 1.26, 95% CI = 1.05–1.51, P = ≤ 0.001, FEM), allelic model (OR = 1.17, 95% CI = 1.03–1.33, P = 0.01, FEM), and CT vs. TT model (OR = 1.23, 95% CI = 1.02–1.49, P = 0.03, FEM).

Subgroup analysis by ethnicity

Finally, we stratified eligible articles according ethnicity including Caucasians (20 articles), and

African-Americans (4 articles). The results showed significant association between IL-4 SNP (C33T) and asthma risk in Causations under recessive model (OR = 1.17, 95% CI = 1.05–1.29, P = ≤ 0.001, FEM), allelic model (OR = 1.13, 95% CI = 1.05–1.21, P = ≤ 0.001, FEM) but not other models. Moreover, there was a significant association between IL-4 SNP (C33T) and risk of asthma in American-African population under dominant model (OR = 1.26, 95% CI = 1.05–1.51, P = ≤ 0.001, FEM), allelic model (OR = 1.17, 95% CI = 1.03–1.33, P = 0.01, FEM), and CT vs. TT model (OR = 1.23, 95% CI = 1.02–1.49, P = 0.03, FEM).

Evaluation of heterogeneity

No significant heterogeneity was detected for IL-4 SNP (C33T) nether in overall population or subgroup analysis (Table 3).

Publication bias

Publication bias was estimated by using funnel plot, Begg's and Egger's tests. No evidence of Publication bias was seen for overall population and subgroup analysis under all genetic models. Additionally, the shape of the funnel plot appeared to be symmetrical which demonstrated that there was no significant publication bias Fig. 3.

Sensitivity analysis

Sensitivity analysis was conducted after sequentially removing each eligible study. This approach is to enumerate as an inevitable step for analyzing multiple criteria. The significance of the pooled ORs was not affected by any single study in the dominant model for IL-4 SNPs, indicating that our results were statistically robust Fig. 4.

Discussion

The cytokine IL-4 act as a key player in the development and pathogenesis of allergic inflammation [37] and atopy [38] through the induction of the heavy chain isotype switching, secretion of IgE antibody (IgE synthesis) by B cells, functioning as a growth factor for Th2 cells [37]. The IL-4 promotes IgE-dependent immune responses as it induces overexpression of IgE receptors on the surface of various immune cells: FcεRI on basophils and mast cells; and FcεRII (CD23) on mononuclear phagocytic cells and B lymphocytes [39]. Thee IL-4 tilts the immune response to anti-inflammatory,

inhibiting macrophages pro-inflammatory effect and downregulating secretion of pro-inflammatory cytokines [40]. The IL-4 critically, initiate immediate allergic responses by triggering IgE-mediated mast cell activation[41]. The IL-4 plays a pivotal role in the priming of naïve T cell towards Th2 differentiation as well as exacerbate allergic inflammation through induction of vascular adhesion molecule 1 (VCAM-1) that recruit leukocytes and promote their survival [39]. The IL-4 induce airway remodeling encountered in asthma by its role in the proliferation of bronchial fibroblasts, myofibroblasts, and airway smooth muscles [38].

At the turn of the millennium genetic polymorphisms of the IL-4 gene in the development and maintenance of asthma have drawn increasing consideration. Modulation of the immune system is the common denominator in IL-4 polymorphisms [40]. Suzuki and coworkers found a single nucleotide polymorphism of C replacement of T at position 33 bp of exon 1 (C + 33T) of the IL-4 proximal promoter region [42]. Asthmatic patients with C + 33T have higher serum level of IL-4 and IgE [43]. Anovazzi and colleagues studied IL-4 haplotypes and reported that the studied haplotypes induce an opposing immune response, as well they recorded minimal functional activity in polymorphisms involving the promoter region [40]. An increasing body of evidence has demonstrated that C + 33T of the IL-4 gene untranslated region (UTR) of chromosome 5q was associated with elevated serum IgE levels and the risk of asthma [44, 45]. However, this association remains inconclusive. If this is indeed the case, a meta-analysis with big sample size, sufficient statistical power, and subgroup analysis was needed.

Our current meta-analysis composed of 24 studies involving 6587 cases and 8408 controls, we systematically assessed the relationship between IL-4 C33T polymorphism and asthma susceptibility. Cumulatively, the result illustrated IL-4 C33T polymorphism as a risk factor in the pathogenesis of asthma. The result indicated that the presence of T allele across different genetic models increased asthma risk by 10–21%. In the subgroup analysis by age, the results rejected the significant association between IL-4 SNP (C33T) and risk of asthma in different age groups except for allelic model, which highlighted the predisposing role of the T allele for the asthma risk in all three age groups. Subgroup analysis by continent revealed a significant association between IL-4 SNP (C33T)

and asthma risk in the European population. In the Asian population, there was a significant association between IL-4 SNP (C33T) and the risk of asthma under recessive and allelic models. In contrast, the American population showed a significant association under dominant and allelic models.

Additionally, Subgroup analysis was conducted according to ethnicity; the results showed a significant association between IL-4 SNP (C33T) and asthma risk in Caucasians under the recessive model and allelic model. On the other hand, there was a significant association between IL-4 SNP (C33T) and the risk of asthma in the American-African population under the dominant model, allelic model, and CT vs. TT model.

It should be noted that our results are not in agreement with those of Liu et al. [29] meta-analysis on the role of IL-4 − C33T variation and asthma. They suggested a significant association between whites and Asians but not among African Americans. While they reported a significant association between the IL-4-C33T polymorphism and asthma risk in the overall population, they did not found a significant association among atopic and non-atopic asthma patients in subgroup analysis. Furthermore, in contrast to our meta-analysis, in the subgroup analysis by age, they reported an increased risk of asthma among children but not in the adult. Finally, while they reported evidence of publication bias, we identified no evidence of publication bias for the overall population and subgroup analysis under all genetic models.

The main reason for these discrepancies raised could be from the fact that Liu and colleagues included 18 studies with 5523 cases and 5618 controls. However, our meta-analysis encompasses 28 studies including 6587 cases and 8408 controls from different ethnicities and continents.

The C33T single nucleotide polymorphism is detected on the 5’ untranslated regions (UTR) of the IL-4 gene [42]. The 5′ UTRs region of mRNA may contain many gene regulatory elements (GRE) that regulate the localization, translation and degradation of transcripts [46]. In the eukaryotic mRNAs, the 5’ UTRs regulate both cap-dependent and cap-independent translation initiation of mRNA [47]. Researchers revealed a relationship between IL-4 C33T polymorphism and elevated serum IgE levels in a group of the Japanese population [48]. While the exact mechanisms by which the IL-4 C33T allele

modulates the gene expression of the IL-4 remain elusive, it has been suggested that this variation may influence the stability of mRNA, as well as transcriptional or translational efficiency of the IL-4 gene, highlighting that the 5’ UTR may involve many cis-acting elements [46, 49, 50].

Heterogeneity and publication bias, which may affect the results of meta-analyses, should always be considered. The result of this study did not show significant heterogeneity. Moreover, there was no significant publication bias in the overall population and subgroup analysis under all genetic models. Consequently, heterogeneity and publication bias did not appear to have inclined the results.

Sensitivity analyses were also performed. There was a little variation of the estimates after exclusion of a single study and the significance of the pooled ORs was not affected proposing the consistency of this result.

The current study had some limitations. First, most included articles were from the Asia continent with Caucasian race and there was no study from Africans; accordingly, the results of this meta-analysis may not be appropriate to Africans. Second, in some studies, the diagnostic criteria and asthma phenotype were not clearly determined; while the asthma diagnostic criteria were primarily based on physical examination, clinical history, and pulmonary function tests (PFT), there did exist a little dissimilarity among studies. Third, the overall results were based on unadjusted estimates; a more precise evaluation should be accompanied when all singular raw data are accessible, which would facilitate the adjustment by other potential co-variants such as; age, gender, obesity, environmental factors, smoking status, and other lifestyles. Fourth, due to a lack of extractable data, we failed to address gene-environment and gene-gene interactions. In contrast to these limitations, two main strengths of our meta-analysis include; Firstly, a large number of patients and the healthy individuals were pooled from various studies, which considerably augment the statistical power of the meta-analysis. Secondly, no evidence of publication biases was identified, representing that the whole collected data may be unbiased.

Conclusion:

Taken together, this study suggests that IL-4 C33T single nucleotide polymorphism potentially acts as a risk factor for asthma in different ethnicities and age groups. Nevertheless, large sample studies

from different continents and races with homogeneous asthmatic patients and well-matched healthy subjects are still needed. Furthermore, gene-environment and gene-gene interactions should also be regarded in future studies. With taking these factors into account in future studies, it would ultimately lead to our comprehensive and better understanding of the association between the IL-4 C33T variation and asthma susceptibility.

Abbreviations

IL-4

interleukin 4

SNP

Single nucleotide polymorphisms

PRISMA

Preferred Reporting Items for Systematic reviews and Meta-Analyses

NOS

Newcastle-Ottawa Scale

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

RR generated the idea. DI analyzed and interpreted the data. GA and BR prepared the original draft. MA, DI, and GA critically revised the paper. RR supervised the project. All authors read and approved

the final manuscript.

Acknowledgement

None.

Disclosure of conflict of interest

None.

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Figures

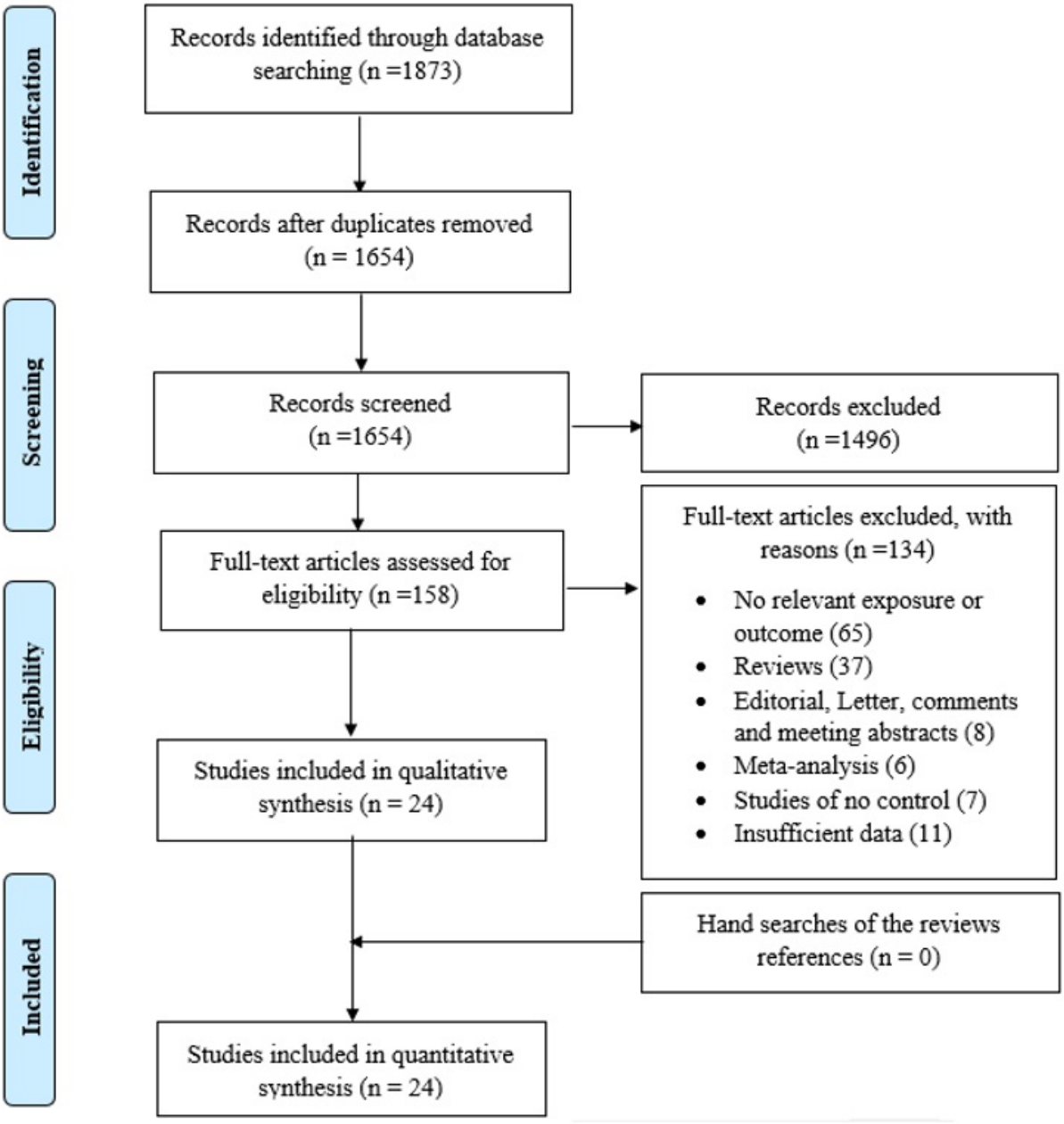

Figure 1

Flow diagram of study selection process

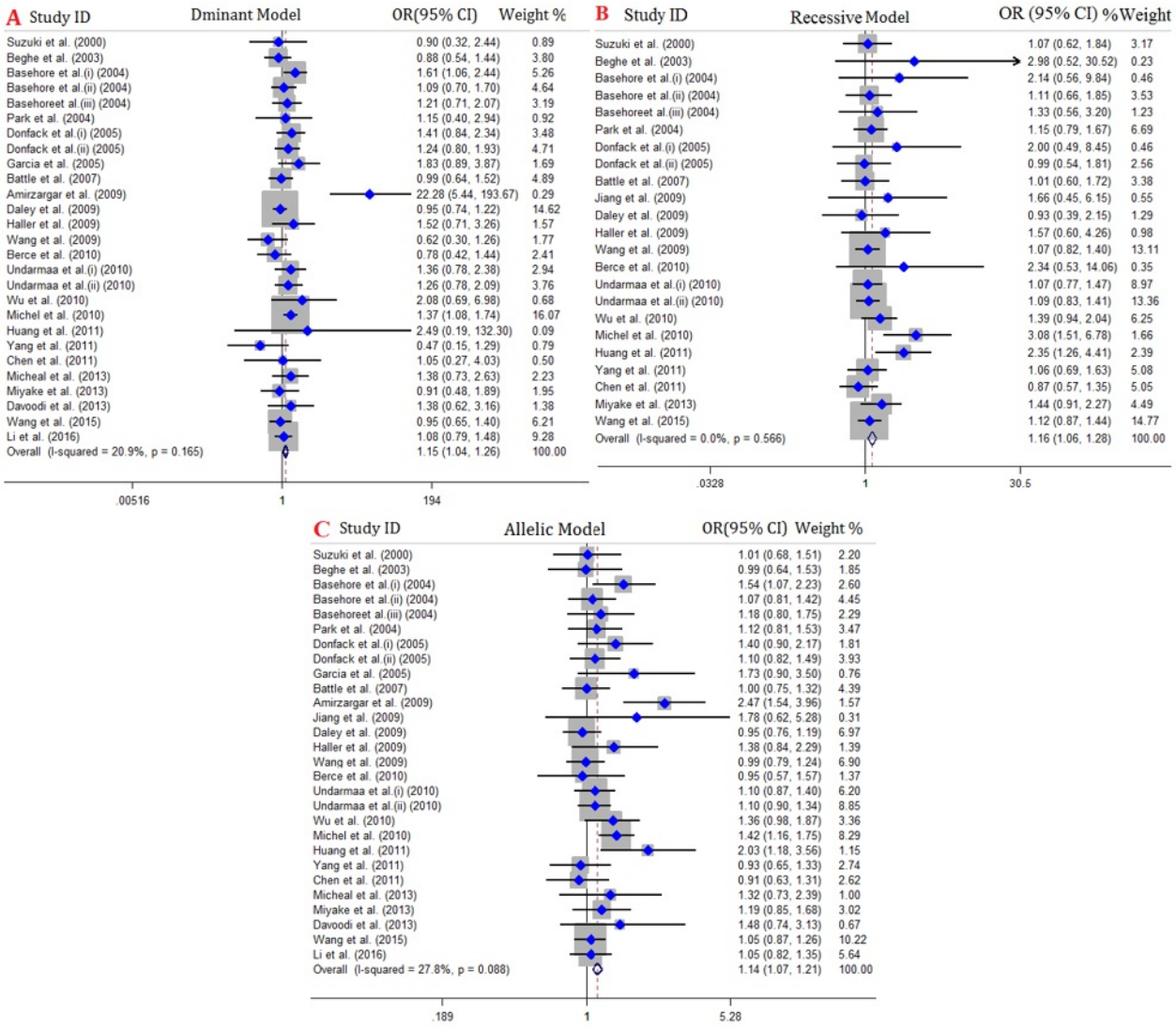

Figure 2

Pooled odds ratio (OR) and 95% confidence interval of individual studies and pooled data for the association between IL-4 C33T gene polymorphism and asthma risk in overall populations for A; dominant model, B; recessive model, C; allelic Model.

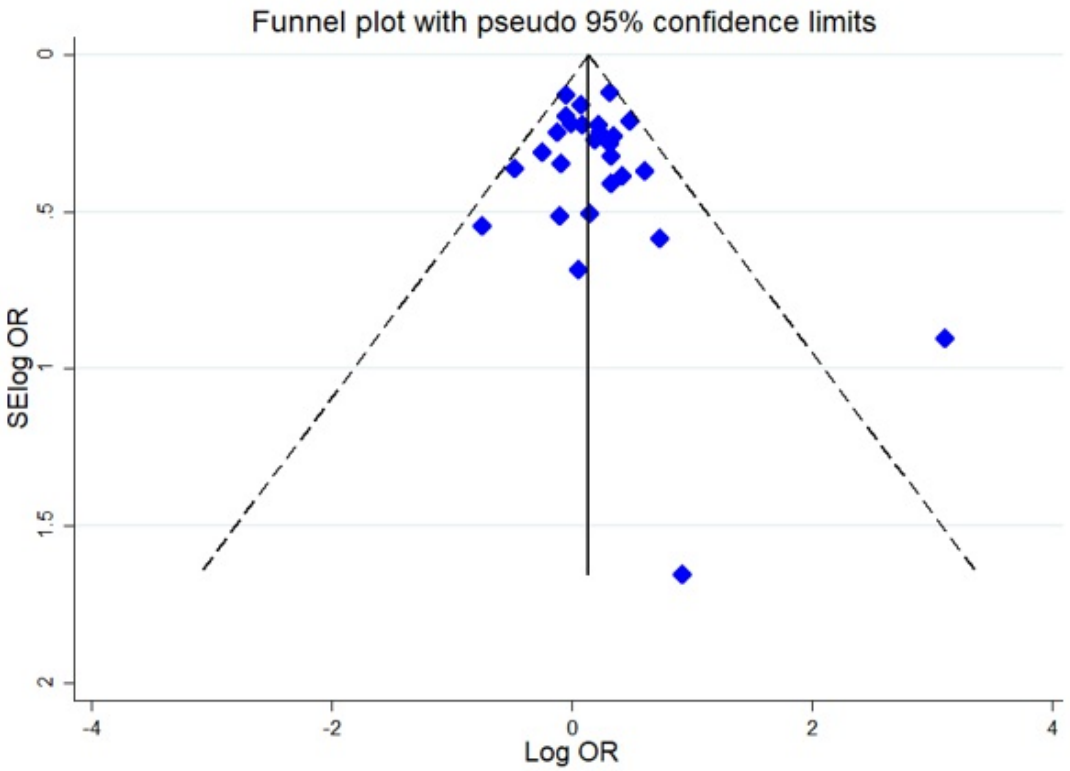

Figure 3

Begg’s funnel plot for publication bias test. Dominant model IL-4 C33T. Each point represents a separate study for the indicated association.

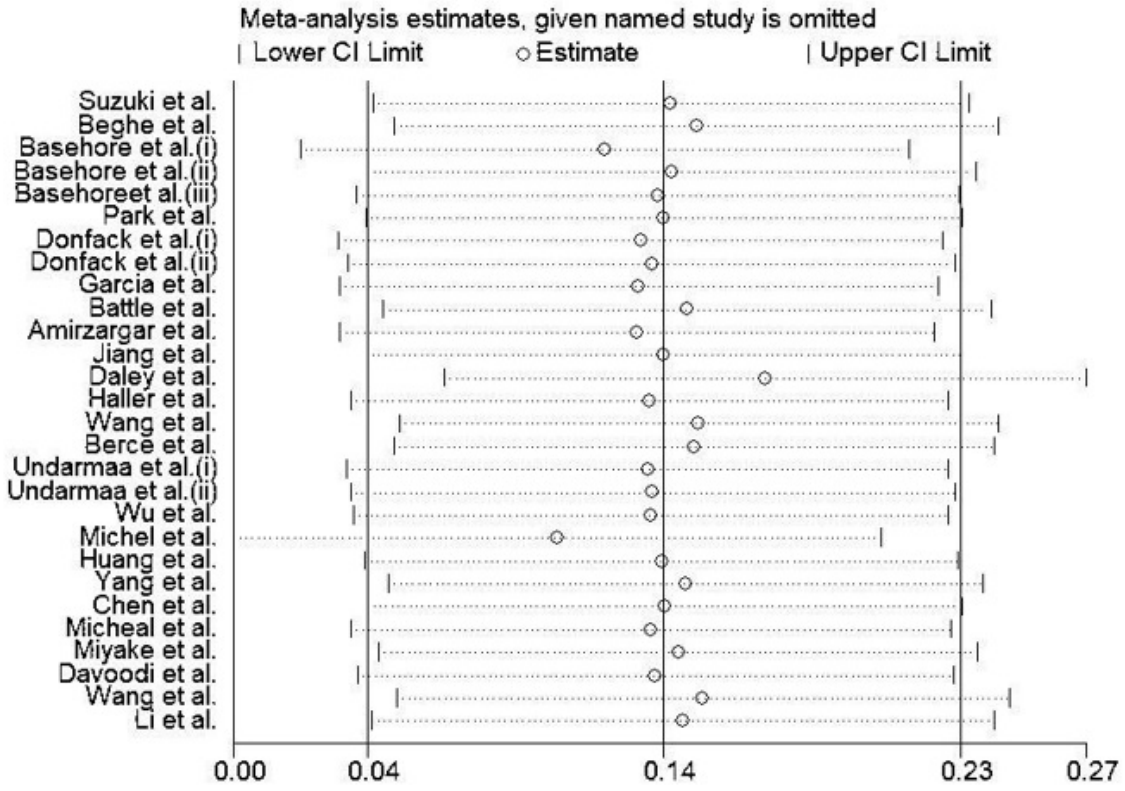

Figure 4

Sensitivity analysis in present meta-analysis investigates the single nucleotide polymorphisms of IL-4 C33T contribute to risk for asthma.