M. Omraninava[1], M. M. Eslami[2], S. Aslani[3], B. Razi[2], D. Imani[4], S. Feyzinia[5,6]

Interleukin 13 gene polymorphism and susceptibility to asthma: a meta-regression and meta-analysis

[1]Department of Infectious Disease, Faculty of Medical Sciences, Sari Branch, Islamic Azad University, Sari, Iran
[2]Department of Hematology, School of Medicine, Tarbiat Modares University, Tehran, Iran
[3]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[5]Tuberclousis and Lung Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[6]Rahat Breath and Sleep Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Key words

Asthma; Meta-analysis; IL-13; polymorphism; genetic susceptibility.

Corresponding author
Sara Feyzinia
Tuberclousis and Lung Diseases Research Center
Tabriz University of Medical Sciences
Golgasht Street
Tabriz, Iran
ORCID ID: N/A
E-mail: Sarafeyzinia@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.180

Impact statement

According to this meta-analysis, IL13 gene rs20541 and rs1800925 polymorphisms were associated with an increased susceptibility to asthma in the overall analysis and in the Caucasian and Asian populations.

Summary

Background*. Previously, lots of studies researched the association of interleukin (IL) 13 gene polymorphisms and the risk of asthma, yielding incongruent outcomes.* ***Objective.*** *To resolve the inconsistency among the different studies, we performed the most up-to-date meta-analysis of IL13 gene rs20541 and rs1800925 polymorphisms and susceptibility to asthma.* ***Methods****. After a systematic literature search up to September 2020, the pooled odds ratio (OR) and their corresponding 95% CI were extracted to determine the association level.* ***Results****. Overall, 45 (containing 10572 cases and 11575 healthy controls) and 31 (containing 10139 cases and 13304 healthy controls) case-control studies for rs20541 and rs1800925 polymorphisms, respectively, were retrieved. Pooled analysis indicated statistically significant association of rs20541 with asthma in the overall analysis. According to the subgroup analysis, significant association was detected between rs20541 polymorphism in European population across dominant model, allelic model, and GA vs GG model. A strongly significant association between rs20541 polymorphism and asthma risk was identified in Asian population under all genetic models except heterozygote model. There was significant association between rs20541 polymorphism and asthma risk in dominant, allelic and heterozygote models for Caucasians. The rs1800925 single-nucleotide polymorphism (SNP) was associated with asthma risk in some genetic models for the overall, Asian, and European populations.* ***Conclusions****. Both rs20541 and rs1800925 polymorphisms of IL13 gene confer a risk factor for asthma in different populations.*

Introduction

Asthma is a chronic inflammatory disorder of the airways that is characterized by reversible airflow obstruction and bronchospasms, affecting 300 million people worldwide and estimated to approach 400 million by 2025 (1, 2). It is a multifactorial disease caused by interactions between multiple genetic and environmental factors, and heritability of asthma has been estimated as 35 to 75% (3, 4). Therefore, genetic susceptibility may play a critical role in the pathogenesis of asthma. A growing body of research has reported more than 100 genes affect predisposing to asthma (5).
T helper (Th) 2 cytokines, including interleukin (IL)-4 and IL1-3 play an important role in the pathogenesis of asthma (6, 7). IL-13 induces many cellular responses, including overexpression of adhesion molecules, antibody class switching to IgE, development of airway hyper-responsiveness (AHR), and proliferation of goblet cells (8, 9). *In vitro* experiments by Walter *et al*. indicated that despite inflammation and Th2 active response, the challenge of IL-13-deficient mice by allergen failed to develop allergen-induced AHR (10). Also, Huang *et al*. demonstrated that IL-13 expression level was raised in the allergen-challenged broncho-alveolar lavage (BAL) of asthmatic patients (11).
The *IL13* gene is located on chromosome 5q31 that codifies for a 13-kDa glycoprotein (12). Two common single nucleotide polymorphisms (SNPs) of *IL13* gene have been studied extensively in susceptibility to asthma (13). The polymorphism of rs20541 (R130Q or Arg130Gln) is located in exon 4, and results in reduced affinity of IL-13 for IL-13 receptor, and enhanced expression of IL-13 in subjects with asthma (14, 15). The other SNP, rs1800925 (1112C/T), is located in the promoter region of *IL13* gene and affects the expression of IL-13 by changing the binding of Signal transducer and activator of transcription (STAT) transcription factors to the promoter region of IL-13 (16, 17). Numerous studies examined the association between these polymorphisms and susceptibility to asthma, but the results are inconsistent and conflicting. As a result, we performed the most up-to-date meta-analysis to determine the association between *IL13* gene rs20541 and rs1800925 polymorphisms and the risk of asthma.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (18). The current meta-analysis does not contain any studies with human participants or animals performed by any of the authors.

Publication search

Two major electronic databases (Scopus and PubMed/Medline) were searched systematically to identify potential studies published up to September 2020. The combination of following key words and Medical Subject Headings (Mesh) terms were applied: ("asthma" (Mesh) OR "asthmatic") AND ("interleukin-13" OR "IL-13" OR "IL13" OR "rs20541" OR "rs1800925") AND ("single nucleotide polymorphism" OR "SNP" OR "polymorphisms" OR "mutation" OR "variation"). No restrictions were placed on language, sample size, population, or publication date. To avoid losing of eligible studies, reference list of the reviews and qualified studies were also scanned.

Inclusion and exclusion criteria

The following inclusion criteria were explored to identify eligible studies: 1) studies evaluating the association between *IL13* gene polymorphism (rs20541 and/or rs1800925) and susceptibility to asthma as the main outcome, 2) subjects diagnosed as having asthma based on the medical history/lung function or the final diagnosis by physician (additionally, we did not distinguish the studies for the grade of asthma severity), 3) studies with sufficient data to extract or calculate odds ratio (OR) and 95% confidence interval (CI), 4) studies which reported genotype distributions and allele frequency and 5) studies with cohort and case-control design. The reviews, meta-analysis, duplicates, case reports, book chapters, and animal studies all were excluded.

Data extraction

Two authors independently and in accordance with a standardized extraction form extracted the following information: the first author's name, 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. Any discrepancies between two authors were solved by discussion.

Quality assessment

We used Newcastle-Ottawa Scale (NOS) in order to evaluate methodological quality of the eligible studies (19). In this scale, selection, comparability of case/controls, exposure/outcome, age and gender were evaluated and scored ranging from 0 to 9 stars. We defined a range in which studies with scores of 0-3, 4-6, or 7-9 was regarded as low, moderate, or high-quality, respectively.

Statistical analysis

We used Pearson's χ^2 test to estimate the deviation from Hardy-Weinberg equilibrium (HWE) in the control group. Pooled OR and 95% CI were calculated to quantitatively evaluate the risk of asthma in the Dominant model (TT + CT *vs* CC), Recessive model (TT *vs* CT + CC), Allelic model (T *vs* C), Homozygote contrast (TT *vs* CC), and Heterozygote contrast (CT *vs* CC) for rs1800925 and Dominant model (AA + GA *vs* GG), Recessive model (AA *vs* GA + GG), Allelic model (A *vs* G), Homozygote contrast (AA *vs* GG), and Heterozygote contrast (GA *vs* GG) for rs20541. Between-study heterogeneity was identified by Q statistics (P-value < 0.1 was considered statistically significant) and I^2-test (I^2 values of 25%, 50%,

and 75% were described as low, moderate, and high heterogeneity, respectively). Studies were pooled using the DerSimonian-Laird algorithm in the presence of heterogeneity (I^2 > 50% and Q statistics < 0.1 (random effects model)) (20). On the other hand, the Mantel-Haenszel algorithm was used in the absence of heterogeneity (I^2 < 50% and Q statistics > 0.1 (fixed effects model)) (21). In order to assess the predefined sources of heterogeneity among included studies, subgroup analysis and meta-regression analysis based on year of population, the continent of the study population, and genotyping method were performed. Publication bias in this study was measured by Egger's regression asymmetry test and Begg's adjusted rank correlation test (21, 22). Finally, to show statistical stableness and the impact of every individual study on the pooled OR, the sensitivity analysis was conducted. Statistically analyses were carried out using STATA (version 14.0; Stata Corporation, College Station, TX) and SPSS (version 23.0; SPSS, Inc. Chicago, IL) software.

Results

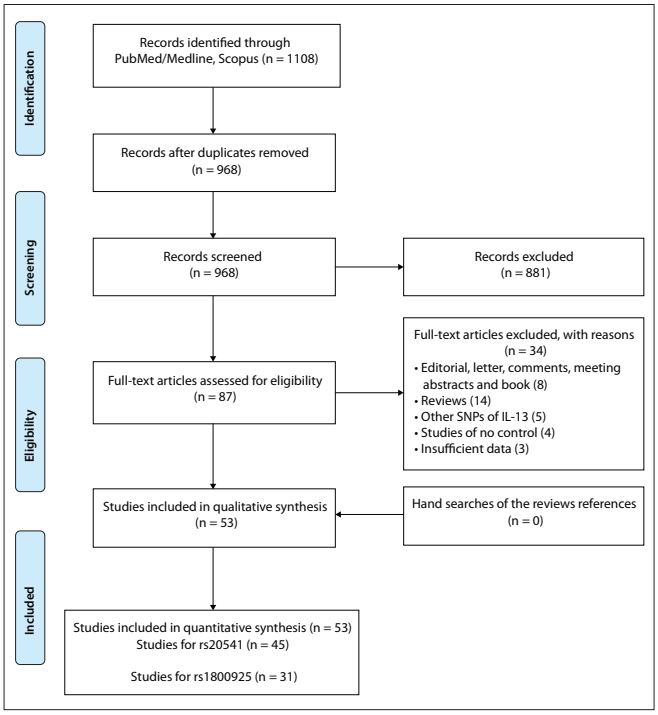
Study selection

The flow chart of implementing the inclusion/exclusion criteria and study selection process is summarized in the **figure 1**. A total of 1108 studies were retrieved from PubMed/Medline and Scopus databases according to the aforementioned key words and Mesh terms. Of them, 140 studies were duplicates and the remaining 968 studies were screened by title and abstract and full text. Finally, 53 publications met the inclusion criteria and were included for quantitative analysis. Of 53 eligible studies, 31 studies evaluated rs1800925 SNP and 45 studies evaluated rs20541 polymorphism. Among the included studies, some of them assessed one SNP (rs1800925 or rs20541) for two different ethnicities in one country and have reported the results in one paper; therefore, we considered them as two case-control studies in the quantitative analysis, but one article in the search strategy. All included studies were conducted between 1999 to 2018 and gained good methodological score, ranging from 5 to 8. Furthermore, case-control design was the most common type among the studies. **Table I** and **II** summarize the characteristics and genotype frequency of the included studies.

Meta-analysis of IL13 gene rs20541 SNP and the risk of asthma

Overall, 45 studies with 10572 cases and 11575 healthy controls were considered eligible and included for the pooled quantitative analysis (23-64). Among these 45 studies, 9 studies were in European countries, 26 studies in Asian countries, 8 studies in American countries, and one study in Africa and one in Oceania. The pooled OR for the association between rs20541 polymorphism and asthma risk revealed a significant correlation under all genotype models and highlighted this SNP as a predisposing factor for asthma: dominant model (OR = 1.18, 95% CI = 1.06-1.31, p < 0.001), recessive model (OR = 1.14, 95% CI = 1.03-1.27, p < 0.001), allelic model (OR = 1.16, 95% CI = 1.07-1.27, p < 0.001), AA *vs* GG model (OR = 1.17, 95% CI = 1.04-1.30, p < 0.001), and GA *vs* GG model (OR = 1.14, 95% CI = 1.02-1.26, p < 0.01; **figure 2**). The results of pooled ORs, heterogeneity tests and publication bias tests in different analysis models are shown in **table III**.

***Figure 1** - Flow diagram of study selection process.*



Subgroup meta-analysis of IL13 gene rs20541 SNP and the risk of asthma

We categorize studies into different subgroups on the basis of continent and ethnicity. The results of pooled ORs, heterogeneity tests and publication bias tests for different analysis models are shown in **table III**. The results of subgroup analysis of rs20541 polymorphism and the risk of asthma based on the continent showed different results. In details, there was no statistically association between rs20541 polymorphism and asthma risk in American population for all genetic models. Significant positive association was detected between rs20541 polymorphism and asthma risk in European population across dominant model (OR = 1.28, 95% CI = 1.06-1.53, p < 0.001), allelic model (OR = 1.17, 95% CI = 1.02-1.35, p = 0.02), and GA *vs* GG model (OR = 1.33, 95% CI = 1.14-1.56, p < 0.001), but not recessive and homozygote model. Furthermore, the results revealed a strong significant association between rs20541 polymorphism and asthma risk in Asian population under all genotype models except heterozygote model.

Table I *- Characteristics of studies included in meta-analysis of overall asthma.*

Study author	Year	Country	Continent	Ethnicity	Mean age Cases/Controls	Total cases / control	Genotyping method	Quality score
***IL13* (rs20541)**								
Hakonarson *et al.*	2001	Iceland	European	Caucasian	38 / NR	94 / 94	Ampli Taq Gold	5
Howard *et al.*	2001	Netherlands	European	Caucasian	52.1 / 51	152 / 120	TaqMan	6
Kauppi *et al.*	2001	Finland	European	Caucasian	NR / NR	163 / 132	Length-multiplexed single-base extension	6
Leung *et al.*	2001	China	Asian	East-Asian	10.3 / 11.4	157 / 54	RFLP-PCR	5
Xi *et al.*	2004	China	Asian	East-Asian	NR / NR	43 / 31	RFLP-PCR	5
Liu *et al.*	2004	China	Asian	East-Asian	NR / NR	100 / 100	RFLP-PCR	6
Donfack *et al.(i)*	2005	USA	American	Mixed	NR / NR	205 / 183	LAS	6
Donfack *et al.(ii)*	2005	USA	American	Mixed	NR / NR	126 / 205	LAS	6
Zhao *et al.*	2005	China	Asian	East-Asian	NR / NR	130 / 100	RFLP-PCR	6
Bernstein *et al.*	2005	USA	American	Mixed	NR / NR	62 / 79	RFLP-PCR	5
Wei *et al.*	2007	China	Asian	East-Asian	NR / NR	32 / 20	RFLP-PCR	5
Hosseini *et al.*	2007	Iran	Asian	Middle-East	34 ± 11 / 33 ± 9	30 / 50	RFLP-PCR	5
Battle *et al.*	2007	USA	American	Mixed	19.4 / 29.9	261 / 174	RFLP-PCR	7
Chan *et al.*	2008	China	Asian	East-Asian	10.4 / 11	273 / 141	RFLP-PCR	6
Kang *et al.*	2008	South Korea	Asian	East-Asian	9.71 ± 2.4 / 10.19 ± 2	374 / 229	RFLP-PCR	7
Kim *et al.*	2008	South Korea	Asian	East-Asian	9.13 ± 2.65 / 10.20 ± 2.68	709 / 227	RFLP-PCR	7
Black *et al.*	2009	UK	European	Caucasian	NR / NR	275 / 2462	Multiplex PCR	8
Daley *et al.*	2009	Australia	Oceania	Caucasian	NR / NR	644 / 750	Illumina Assay	8
Jiang *et al.*	2009	China	Asian	East-Asian	NR / NR	24 / 24	RFLP-PCR	5
Lianes *et al.*	2009	Spain	European	Caucasian	22.98 / 37.6	108 / 50	RFLP-PCR	5
Wang *et al.*	2009	Taiwan	Asian	East-Asian	7.82 ± 3.81 / 8.37 ± 2.45	446 / 505	TaqMan	8
Bottema *et al.*	2010	Dutch	European	Caucasian	31.8 ± 8.3 / 26.9 ± 5.4	114 / 89	Mass Array	5
Wu *et al.*	2010	China	Asian	East-Asian	8.8 / 9.2	252 / 227	RFLP-PCR	7
Yang *et al.*	2010	China	Asian	East-Asian	NR / NR	178 / 158	NR	6
Zdorova *et al.*	2010	Russia	European	Caucasian	NR / NR	283 / 227	MALDI-TOF mass spectrometry	7
Palikhe *et al.*	2010	Korea	Asian	East-Asian	42.29 ± 13.2 / 33.46 ± 14	463 / 430	SNAP shot	8
Undarmaa *et al.(i)*	2010	Japan	Asian	East-Asian	9.9 / 9.3	325 / 339	TaqMan	7
Undarmaa *et al.(ii)*	2010	Japan	Asian	East-Asian	45 / 43.2	367 / 676	TaqMan	8
Baye *et al.(i)*	2011	USA	American	Mixed	10.1 / 12	413 / 298	IGGAS	7
Baye *et al.(ii)*	2011	USA	American	Mixed	10.3 / 11.4	315 / 51	IGGAS	5
Yang *et al.*	2011	China	Asian	East-Asian	41.59 / 41.16	201 / 203	MALDI-TOF	6
Munoz *et al.*	2012	Mexico	American	Mixed	7.24 / 7.28	90 / 105	TaqMan	5
Liu *et al.*	2013	China	Asian	East-Asian	3-12 / 18.35	384 / 384	TaqMan	7
Shazia *et al.*	2013	Pakistan	Asian	South-Asian	NR / NR	214 / 120	RFLP-PCR	6

→

Study author	Year	Country	Continent	Ethnicity	Mean age Cases/Controls	Total cases / control	Genotyping method	Quality score
Berenguer *et al.*	2014	Portugal	European	Caucasian	NR / NR	98 / 105	TaqMan	6
Aguilar *et al.*	2014	Mexico	American	Mixed	10.8 ± 2.9 / NR	421 / 430	TaqMan	8
Ramphul *et al.*	2015	Mauritius	African	African	17.1 / 18.22	189 / 189	TaqMan	7
Davoodi *et al.*	2015	India	Asian	South-Asian	NR / NR	100 / 50	Mass Array	6
Hua *et al.*	2015	China	Asian	East-Asian	4.9 / 23.32	1000 / 1000	TaqMan	8
Resende *et al.*	2016	Poland	European	Caucasian	11.5 / 12.1	147 / 192	RFLP-PCR	6
Wan *et al.*	2016	China	Asian	East-Asian	39.32 / 56.06	103 / 125	TaqMan	5
Adjers *et al.*	2017	Singapore	Asian	Southeast -Asian	10.3 ± 8.2 / 10.0 ± 9.1	118 / 70	TaqMan	5
Alasandagutti *et al.*	2017	India	Asian	South-Asian	NR / NR	120 / 120	RFLP-PCR	5
Halwani *et al.*	2017	Saudi Arabia	Asian	Middle-East	NR / NR	232 / 228	Sanger-sequenced	6
Zhang *et al.*	2018	China	Asian	East-Asian	9.00 ± 2.78/ 8.21 ± 2.72	37 / 29	TaqMan	5
***IL13* (rs1800925)**								
Kraan *et al.*	1999	Netherlands	European	Caucasian	NR / NR	101 / 107	EMSA	5
Howard *et al.*	2001	Netherlands	European	Caucasian	52.1 / 51	171 / 119	TaqMan	6
Donfack *et al.(i)*	2005	USA	American	Mixed	NR / NR	126 / 205	LAS	6
Donfack *et al.(ii)*	2005	USA	American	Mixed	NR / NR	205 / 183	LAS	6
Moissidis *et al.*	2005	USA	American	Mixed	NR / NR	61 / 157	RFLP-PCR	5
Battle *et al.*	2007	USA	American	Mixed	24.5 /29.9	261 / 174	RFLP-PCR	7
Kang *et al.*	2008	South Korea	Asian	East-Asian	9.71 ± 2.42 / 10.19 ± 2.91	374 / 241	RFLP-PCR	7
Kim *et al.*	2008	South Korea	Asian	East-Asian	9.13 ± 2.65 / 10.20 ± 2.68	716 / 241	RFLP-PCR	7
Black *et al.*	2009	UK	European	Caucasian	NR / NR	263 / 2362	Multiplex PCR	8
Daley *et al.*	2009	Australia	Oceania	Caucasian	NR / NR	642 / 751	Illumina Assay	8
Wang *et al.*	2009	Taiwan	Asian	East-Asian	7.820 ± 3.81 / 8.37 ± 2.45	446 / 511	TaqMan	8
Lianes *et al.*	2009	Spain	European	Caucasian	22.9 /37.6	109 / 50	RFLP-PCR	5
Bottema *et al.*	2010	Netherlands	European	Caucasian	31.8 ± 8.3 / 26.9 ± 5.4	115 / 92	Mass ARRAY	5
Dewan *et al.*	2010	USA	American	Mixed	NR / NR	104 / 503	Affymetrix	7
Zdorova *et al.*	2010	Russia	European	Caucasian	NR / NR	283 / 227	MALDI-TOF	7
Undarmaa *et al.*	2010	Japan	Asian	East-Asian	9.9 / 9.3	325 / 336	TaqMan	7
Wu *et al.*	2010	China	Asian	East-Asian	8.8 / 9.2	252 / 227	PCR-RFLP	7
Baye *et al.(i)*	2011	USA	American	Mixed	NR / NR	413 / 298	IGGAS	7
Baye *et al.(ii)*	2011	USA	American	Mixed	NR / NR	315 / 51	IGGAS	5
Noguch *et al.*	2011	Japan	Asian	East-Asian	NR / NR	938 / 2376	GWAS	8
Yang *et al.*	2011	China	Asian	East-Asian	41.59 / 41.16	193 / 204	MALDI-TOF	6
Munoz *et al.*	2012	Mexico	American	Mixed	7.20 ± 0.9 / 7.5 ± 0.86	90 / 111	TaqMan	5
Liu *et al.*	2012	China	Asian	East-Asian	3.12 / 18.36	384 / 384	TaqMan	7
Dixit *et al.*	2014	India	Asian	South-Asian	6.29 ± 3.28 / 6.08 ± 3.22	275 / 275	RFLP-PCR	7
Li *et al.*	2014	China	Asian	East-Asian	8.4 ± 2.7 / 7.9 ± 3.2	491 / 505	TaqMan	8
Aguilar *et al.*	2014	Mexico	American	Mixed	10.8 ± 2.9 / NR	421 / 430	TaqMan	8

Study author	Year	Country	Continent	Ethnicity	Mean age Cases/Controls	Total cases / control	Genotyping method	Quality score
Li *et al.*	2015	China	Asian	East-Asian	5 / 5.06	652 / 752	SNaP Shot Assay	8
Ramphul *et al.*	2015	Mauritius	African	African	12.4 / 18.22	190 / 187	TaqMan	6
Hua *et al.*	2015	China	Asian	East-Asian	4.9 / 23.32	1000 / 1000	TaqMan	8
Wan *et al.*	2016	China	Asian	South-Asian	10.32 ± 8.23 / 10.09 ± 9.16	103 / 125	RFLP-PCR	5
Alasandagutti *et al.*	2017	India	Asian	South-Asian	34.1 / 34.1	120 / 120	RFLP-PCR	5

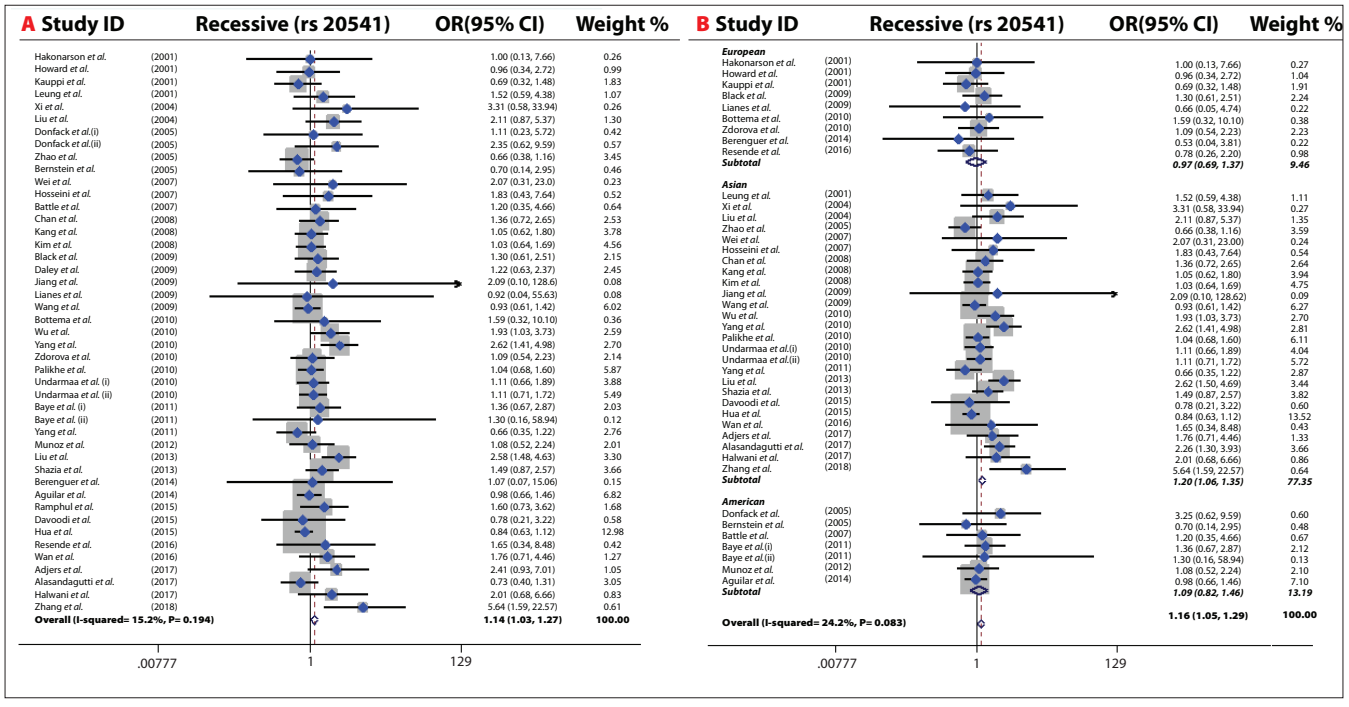
NR: not reported.

For more detailed information, we stratified the included studies based on ethnicity. According to this subgroup, people with mixed ethnicity which were mostly combination of Caucasians, Latins, and American-Africans were not affected by rs20541 polymorphism. However, there was significant association between rs20541 polymorphism and asthma risk in dominant, allelic and heterozygote models for Caucasian population. Eventually we categorized Asian populations to East-Asian, South-Asian and Middle-East. Interestingly, significant associations were observed in the South-Asian and Middle-East populations, but no significant association was observed between rs20541 polymorphism and asthma risk in East-Asian populations (**table III**).

Meta-analysis of IL13 gene rs1800925 SNP and the risk of asthma

Overall, 31 studies containing 10139 cases and 13304 healthy controls were included to evaluate the association between *IL13* gene rs1800925 polymorphism and asthma risk (24, 29, 33, 35-38, 41-45, 47, 48, 50, 51, 54, 55, 59, 61, 65-71). Of which, 6 studies were in European countries, 14 studies were in Asian countries, 9 studies were in American countries, 1 study in Africa, and 1 in Oceania. The results of overall pooled analysis indicated no significant association between *IL13* gene rs1800925 polymorphism and asthma risk under four genotype models. However, a protective significant association was observed just in

Figure 2 - *Pooled odds OR and 95% confidence interval of individual studies and pooled data for the association IL-13 rs20541 polymorphism and the risk of asthma in overall populations and subgroup analysis for A: recessive model (overall population); B: recessive model (subgroup analysis).*



recessive model (OR = 0.85, 95% CI = 0.78-0.94, p < 0.001). **Figure 3** shows the overall analysis and subgroup analysis of *IL13* gene rs1800925 SNP in the dominant model.

Subgroup meta-analysis of IL13 gene rs1800925 SNP and the risk of asthma

Similar to rs20541, we stratified eligible studies based on the continent which studies were performed as well as the ethnicity. The analyses demonstrated that rs1800925 was not significantly associated with the risk of asthma in the American population. However, significant association was detected for European populations under dominant model (OR = 1.52, 95% CI = 1.24-1.86, p < 0.001), allelic model (OR = 1.40, 95% CI = 1.02-1.90, p = 0.03), and CT *vs* CC model (OR = 1.51, 95% CI = 1.23-1.87, p < 0.001), but not recessive and homozygote models. In addition, rs1800925 SNP was detected as a protective SNP in Asians for the TT *vs* CC (OR = 0.82, 95% CI = 0.69-0.97, p = 0.02) and the recessive models (OR = 0.81, 95% CI = 0.71-0.91, p < 0.001). Furthermore, ethnicity-specific subgroup indicated associations between rs1800925 and asthma risk in Caucasians (dominant model (OR = 1.37, 95% CI = 1.03-1.82, p = 0.03), TC *vs* CC model (OR = 1.33, 95% CI = 1.03-1.72, p = 0.03)), East-Asians (recessive model (OR = 0.82, 95% CI = 0.72-0.93, p < 0.001), TT *vs* CC model (OR = 0.79, 95% CI = 0.65-0.95, p = 0.01)), South-Asians (TC *vs* CC model (OR = 2.91, 95% CI = 1.17-7.21, p = 0.03)), but not countries with mixed ethnicity (**table III**).

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 for the dominant model of rs1800925 and rs20541 SNPs appeared to be symmetrical, demonstrating that there was no significant publication bias (**figure 4**).

Sensitivity analysis

Sensitivity analysis was conducted after successive omission of each eligible study. The significance of the pooled ORs was not affected by any single study, indicating that our results were statistically robust (**figure 5**).

Meta-regression analyses

Meta-regression analyses were performed to explore potential sources of heterogeneity among included studies (**table IV**). The findings indicated that none of the expected heterogeneity parameters were the source of heterogeneity (**figure 6**).

Discussion

Up to now, numerous replication case-control investigations have tried to decipher the association of *IL13* gene polymorphisms and risk of asthma. That notwithstanding, these disperse investigation demonstrated incongruous reports. Diversity in the race of included populations, heterogenicity in the diagnostic criteria of the diseases, lack of statistical power, limited sample sizes, and the linkage disequilibrium (LD) between different genes or variations may be the underlying cause of such conflicting observations (72).

Figure 3 *- Pooled odds OR and 95% confidence interval of individual studies and pooled data for the association IL-13 rs1800925 polymorphism and the risk of asthma in overall populations and subgroup analysis for A: Dominant model (overall population); B: Dominant model (subgroup analysis).*

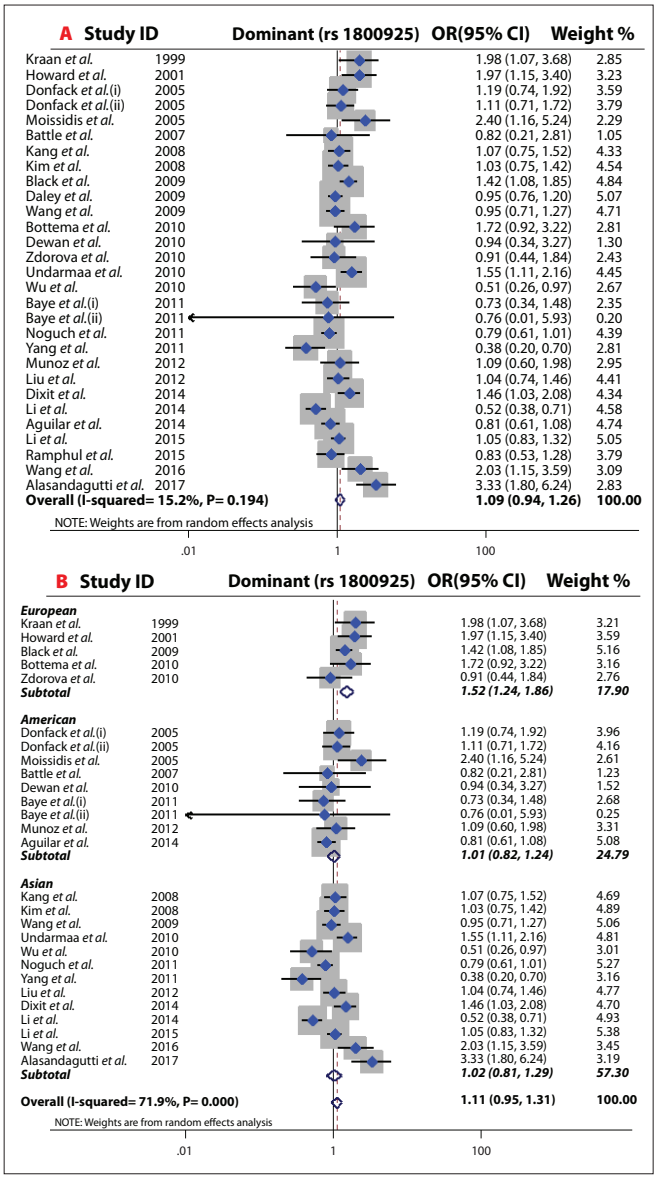


Table II *- Distribution of genotype and allele among asthma patients and controls.*

Study author	Asthma cases					Healthy control					P-HWE	MAF
	GG	GA	AA	G	A	GG	GA	AA	G	A		
***IL13* (rs20541)**												
Hakonarson *et al.*	66	25	3	157	31	64	27	3	155	33	0/94	0/175
Howard *et al.*	89	52	11	230	74	67	44	9	178	62	0/63	0/258
Kauppi *et al.*	64	82	17	210	116	62	51	19	175	89	0/11	0/337
Leung *et al.*	54	74	29	182	132	21	26	7	68	40	0/81	0/37
Xi *et al.*	10	25	8	45	41	16	13	2	45	17	0/76	0/274
Liu *et al.*	27	54	19	108	92	44	46	10	134	66	0/68	0/33
Donfack *et al.(i)*	132	68	5	332	78	126	53	4	305	61	0/56	0/166
Donfack *et al.(ii)*	78	41	7	197	55	127	73	5	327	83	0/14	0/202
Zhao *et al.*	18	60	52	96	164	8	42	50	58	142	0/84	0/71
Bernstein *et al.*	32	26	4	90	34	48	24	7	120	38	0/13	0/24
Wei *et al.*	18	8	6	44	20	15	3	2	33	7	0/03	0/175
Hosseini *et al.*	11	13	6	35	25	34	10	6	78	22	0/003	0/22
Battle *et al.*	171	81	9	423	99	117	52	5	286	62	0/78	0/178
Chan *et al.*	94	136	43	324	222	54	70	17	178	104	0/43	0/368
Kang *et al.*	160	166	48	486	262	101	100	28	302	156	0/67	0/34
Kim *et al.*	301	318	90	920	498	99	100	28	298	156	0/72	0/343
Black *et al.*	166	98	11	430	120	1729	657	76	4115	809	0/16	0/164
Daley *et al.*	426	196	22	1048	240	520	209	21	1249	251	0/99	0/167
Jiang *et al.*	20	2	2	42	6	18	5	1	41	7	0/42	0/145
Lianes *et al.*	68	38	2	174	42	41	8	1	90	10	0/43	0/1
Wang *et al.*	203	194	49	600	292	212	234	59	658	352	0/64	0/348
Bottema *et al.*	57	51	6	165	63	62	24	3	148	30	0/72	0/168
Wu *et al.*	105	111	36	321	183	125	84	18	334	120	0/46	0/264
Yang *et al.*	71	60	47	202	154	73	66	19	212	104	0/49	0/329
Zdorova *et al.*	144	116	23	404	162	125	85	17	335	119	0/62	0/262
Palikhe *et al.*	207	200	56	614	312	206	174	50	586	274	0/15	0/318
Undarmaa *et al.(i)*	145	144	36	434	216	156	149	34	461	217	0/85	0/32
Undarmaa *et al.(ii)*	166	162	39	494	240	322	289	65	933	419	0/98	0/309
Baye *et al.(i)*	230	157	26	617	209	183	101	14	467	129	0/98	0/216
Baye *et al.(ii)*	220	87	8	527	103	36	14	1	86	16	0/78	0/156
Yang *et al.*	105	73	23	283	119	90	80	33	260	146	0/03	0/359
Munoz *et al.*	17	52	21	86	94	17	65	23	99	111	0/01	0/528
Liu *et al.*	180	154	50	514	254	199	164	21	562	206	0/08	0/268
Shazia *et al.*	81	64	69	226	202	47	44	29	138	102	< 0.001	0/425
Berenguer *et al.*	69	27	2	165	31	71	32	2	174	36	0/45	0/171
Aguilar *et al.*	156	202	63	514	328	176	189	65	541	319	0/22	0/37
Ramphul *et al.*	93	76	20	262	116	83	93	13	259	119	0/05	0/314
Davoodi *et al.*	89	3	8	181	19	45	0	5	90	10	< 0.001	0/1

Study author	Asthma cases					Healthy control					P-HWE	MAF
	GG	GA	AA	G	A	GG	GA	AA	G	A		
Hua *et al.*	470	423	107	1363	637	390	486	124	1266	734	0/14	0/367
Resende *et al.*	92	50	5	234	60	136	52	4	324	60	0/7	0/156
Wan *et al.*	43	45	15	131	75	71	43	11	185	65	0/23	0/26
Adjers *et al.*	28	65	25	121	115	34	29	7	97	43	0/82	0/307
Alasandagutti *et al.*	67	19	34	153	87	43	35	42	121	119	< 0.001	0/495
Halwani *et al.*	141	79	12	361	103	175	47	6	397	59	0/19	0/129
Zhang *et al.*	7	10	20	24	50	11	13	5	35	23	0/73	0/396
Study author	**Asthma cases**					**Healthy control**					**P-HWE**	**MAF**
	CC	**CT**	**TT**	**C**	**T**	**CC**	**CT**	**TT**	**C**	**T**		
***IL13* (rs1800925)**												
Kraan *et al.*	57	31	13	145	57	77	28	2	182	32	0/76	0/149
Howard *et al.*	99	63	9	261	81	87	30	2	204	34	0/74	0/142
Donfack *et al.(i)*	72	42	12	186	66	126	71	8	323	87	0/6	0/212
Donfack *et al.(ii)*	69	100	36	238	172	66	85	32	217	149	0/6	0/407
Moissidis *et al.*	13	36	12	62	60	62	75	20	199	115	0/71	0/366
Battle *et al.*	9	81	171	99	423	5	52	117	62	286	0/78	0/821
Kang *et al.*	236	128	10	600	148	156	79	6	391	91	0/27	0/188
Kim *et al.*	455	236	25	1146	286	155	80	6	390	92	0/24	0/19
Black *et al.*	158	98	7	414	112	1609	673	80	3891	833	0/35	0/176
Daley *et al.*	425	195	22	1045	239	490	234	27	1214	288	0/88	0/191
Wang *et al.*	321	113	12	755	137	357	136	18	850	172	0/26	0/168
Lianes *et al.*	36	53	20	125	93	17	14	19	48	52	< 0.001	0/52
Bottema *et al.*	67	43	5	177	53	65	23	4	153	31	0/3	0/168
Dewan *et al.*	5	34	65	44	164	23	171	309	217	789	0/91	0/784
Zdorova *et al.*	23	116	144	162	404	17	85	125	119	335	0/62	0/737
Undarmaa *et al.*	186	119	20	491	159	227	98	11	552	120	0/91	0/178
Wu *et al.*	36	111	105	183	321	18	84	125	120	334	0/46	0/735
Baye *et al.(i)*	26	157	230	209	617	14	101	183	129	467	0/98	0/783
Baye *et al.(ii)*	8	87	220	103	527	1	14	36	16	86	0/78	0/843
Noguch *et al.*	113	438	387	664	1212	232	1033	1111	1497	3255	0/71	0/684
Yang *et al.*	144	43	6	331	55	148	50	6	346	62	0/48	0/151
Munoz *et al.*	45	34	11	124	56	58	46	7	162	60	0/59	0/27
Liu *et al.*	285	84	15	654	114	288	80	16	656	112	< 0.001	0/145
Dixit *et al.*	109	121	45	339	211	135	77	63	347	203	0	0/369
Li *et al.*	400	85	6	885	97	353	143	9	849	161	0/2	0/159
Aguilar *et al.*	202	177	42	581	261	185	189	56	559	301	0/48	0/35
Li *et al.*	450	187	15	1087	217	527	208	17	1262	242	0/5	0/16
Ramphul *et al.*	120	61	9	301	79	110	69	8	289	85	0/48	0/227
Hua *et al.*	683	282	35	1648	352	685	281	34	1651	349	0/43	0/174
Wan *et al.*	48	42	13	138	68	80	38	7	198	52	0/38	0/208
Alasandagutti *et al.*	67	41	12	175	65	97	12	11	206	34	0	0/141

P-HWE: P-value for Hardy-Weinberg equilibrium; MAF: minor allele frequency of control group.

Table III *- Main results of pooled ORs in meta-analysis of IL13 gene polymorphisms in asthma patients.*

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
IL13 (rs20541)										
Overall	Dominant model		1.18	1.06 - 1.31 (< 0.001)	59.3	< 0.001	1.09	0.27	2.59	0.01
	Recessive model		1.14	1.03 - 1.27 (< 0.001)	15.1	0.19	1.25	0.21	2.04	0.04
	Allelic model	10572 / 11575	1.16	1.07 - 1.27 (< 0.001)	63.3	< 0.001	1.52	0.12	3.09	0.004
	AA *vs* GG		1.117	1.04 - 1.30 (< 0.001)	36.4	0.06	0.97	0.33	2.48	0.01
	GA *vs* GG		1.14	1.02 - 1.26 (0.01)	53.2	< 0.001	0.16	0.87	1.67	0.10
Subgroup by continent										
Asian	Dominant model		1.20	1.04 - 1.38 (0.01)	62	< 0.001	1.70	0.09	3.09	0.005
	Recessive model		1.20	1.06 - 1.35 (< 0.001)	47.9	< 0.001	1.92	0.05	2.47	0.01
	Allelic model	6441 / 5767	1.22	1.08 - 1.38 (< 0.001)	71.7	< 0.001	1.83	0.06	3.51	0.002
	AA *vs* GG		1.20	1.05 - 1.36 (0.007)	54.1	< 0.001	1.65	0.09	3.11	0.005
	vs		1.02	0.94 - 1.11 (0.65)	53.1	0.83	0.75	0.45	1.96	0.06
European	Dominant model		1.28	1.06 - 1.53 (< 0.001)	26.6	0.20	0	1	0.62	0.55
	Recessive model		0.97	0.69 - 1.37 (0.87)	0	0.96	- 1.25	0.21	- 0.66	0.53
	Allelic model	1463 / 3568	1.17	1.02 - 1.35 (0.02)	19.7	0.26	-0.83	0.40	- 0.77	0.46
	AA *vs* GG		1.09	0.77 - 1.56 (0.61)	0	0.96	- 1.25	0.21	- 0.92	0.39
	GA *vs* GG		1.33	1.14 - 1.56 (< 0.001)	27.7	0.19	0	1	- 0.41	0.69
American	Dominant model		1.15	0.97 - 1.35 (0.10)	0	0.93	- 1.35	0.17	- 1.11	0.31
	Recessive model		1.09	0.82 - 1.46 (0.55)	0	0.90	0.45	0.65	0.97	0.37
	Allelic model	1688 / 1342	1.10	0.97 - 1.25 (0.12)	0	0.93	0.15	0.88	- 0.44	0.67
	AA *vs* GG		1.17	0.85 - 1.61 (0.32)	0	0.94	0.45	0.65	0.54	0.61
	GA *vs* GG		1.14	0.96 - 1.35 (0.14)	0	0.83	- 0.45	0.65	- 0.86	0.43
Subgroup by Ethnicity										
Caucasian	Dominant model		1.25	1.11 - 1.42 (< 0.001)	22.8	0.23	0.27	0.78	- 0.07	0.94
	Recessive model		1.02	0.75 - 1.38 (0.89)	0	0.97	- 1.70	0.08	- 0.96	0.36
	Allelic model	2107/ 4318	1.17	1.04 - 1.31 (< 0.001)	11.2	0.34	- 0.63	0.53	- 0.47	0.65
	AA *vs* GG		1.13	0.83 - 1.54 (0.43)	0	0.97	- 1.52	0.12	- 1.16	0.28
	GA *vs* GG		1.27	1.12 - 1.45 (< 0.001)	26.4	0.20	0.45	0.65	0.21	0.84
Mixed	Dominant model		1.15	0.97 - 1.35 (0.10)	0	0.93	- 1.35	0.17	- 1.11	0.31
	Recessive model		1.09	0.82 - 1.46 (0.55)	0	0.90	0.45	0.65	0.97	0.37
	Allelic model	1688 / 1342	1.10	0.97 - 1.25 (0.12)	0	0.93	0.15	0.88	- 0.44	0.67
	AA *vs* GG		1.17	0.85 - 1.61 (0.32)	0	0.94	0.45	0.65	0.54	0.61
	GA vs GG		1.14	0.96 - 1.35 (0.14)	0	0.83	- 0.45	0.65	- 0.86	0.43
East-Asian	Dominant model		1.02	0.94 - 1.10 (0.69)	57.8	< 0.001	1.49	0.13	2.44	0.02
	Recessive model		1.13	0.99 - 1.29 (0.06)	51.7	< 0.001	2.21	0.2	2.70	0.01
	Allelic model	5642 / 5074	1.14	1 - 1.29 (0.04)	70.1	< 0.001	1.56	0.11	2.76	0.01
	AA *vs* GG		1.13	0.98 - 1.30 (0.09)	59.1	< 0.001	1.69	0.09	2.61	0.01
	GA *vs* GG		0.98	0.90 - 1.07 (0.71)	39.5	0.03	0.39	0.69	1.620	0.12
Middle-East	Dominant model		2.30	1.55 - 3.41 (< 0.001)	0	0.35	1	0.31	-	-

→

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
	Recessive model		1.94	0.79 - 4.74 (0.14)	0	0.92	- 1	0.31	-	-
	Allelic model	262 / 278	2.01	1.45 - 2.80 (< 0.001)	0	0.51	1	0.31	-	-
	AA *vs* GG		2.68	1.07 - 6.72 (0.03)	0	0.82	- 1	0.31	-	-
	GA *vs* GG		2.25	1.48 - 3.43 (< 0.001)	0.6	0.31	- 1	0.31	-	-
South-Asian	Dominant model		1.16	0.81 - 1.67 (0.40)	0	0.79	0.52	0.60	0.10	0.93
	Recessive model		1.71	1.18 - 2.49 (< 0.001)	19.8	0.28	- 0.52	0.60	- 1.06	0.48
	Allelic model	434 / 290	1.36	1.01 - 1.83 (0.04)	24.2	0.26	0.52	0.60	- 0.41	0.57
	AA *vs* GG		1.51	1 - 2.30 (0.51)	0	0.48	- 0.52	0.60	- 1.13	0.46
	GA *vs* GG		0.78	0.49 - 1.23 (0.28)	0	0.64	- 1	0.31	-	-
IL13 (rs1800925)										
Overall	Dominant model		1.09	0.94 - 1.26 (0.15)	70.3	< 0.001	0.54	0.58	0.95	0.35
	Recessive model		0.85	0.78 - 0.94 (< 0.001)	21.9	0.14	3.17	0.002	4.18	0.005
	Allelic model	10139/ 13304	1.04	0.95 - 1.15 (0.37)	70.1	< 0.001	2.48	0.01	3.03	0.005
	TT *vs* CC		0.90	0.79 - 1.03 (0.08)	29.8	0.06	2.21	0.02	3.47	0.003
	TC *vs* CC		1.11	0.98 - 1.27 (0.10)	61.9	< 0.001	0.68	0.49	0.98	0.33
Subgroup by continent										
Asian	Dominant model		1.02	0.81 - 1.29 (0.84)	81.6	< 0.001	0.73	0.46	0.46	0.65
	Recessive model		0.81	0.71 - 0.91 (< 0.001)	18.7	0.25	1.83	0.06	2.04	0.06
	Allelic model	5254/ 6251	1	0.84 - 1.18 (0.96)	81.2	< 0.001	0.61	0.54	1.48	0.16
	TT *vs* CC		0.82	0.69 - 0.97 (0.02)	50.9	0.01	1.46	0.14	1.66	0.12
	TC *vs* CC		1.06	0.84 -1.36 (0.61)	81.1	< 0.001	1.10	0.27	0.81	0.43
European	Dominant model		1.52	1.24 - 1.86 (< 0.001)	0	0.41	- 0.21	0.83	0.70	0.50
	Recessive model		0.93	0.67 - 1.28 (0.63)	42.5	0.13	2.71	0.002	5.21	0.001
	Allelic model	933 / 2907	1.40	1.02 - 1.90 (0.03)	70.9	< 0.001	1.88	0.06	2.44	0.04
	TT *vs* CC		1.16	0.70 - 1.90 (0.56)	42.7	0.13	0.21	0.83	1.44	0.19
	TC *vs* CC		1.51	1.23 - 1.87 (< 0.001)	0	0.74	- 0.42	0.67	0.66	0.53
American	Dominant model	1996 / 2112	1.01	0.82 - 1.24 (0.90)	10.1	0.35	- 0.98	0.32	0.31	0.77
	Recessive model		0.94	0.79 - 1.11 (0.46)	18.5	0.27	1.96	0.05	1.91	0.15
	Allelic model		1.01	0.87 - 1.18 (0.85)	39.6	0.10	0.98	0.32	1.53	0.22
	TT *vs* CC		0.99	0.75 - 1.32 (0.97)	34.9	0.13	1.96	0.05	3.01	0.05
	TC *vs* CC		0.98	0.81 - 1.19 (0.86)	0	0.65	- 0.98	0.32	- 0.07	0.94
Subgroup by Ethnicity										
Caucasian	Dominant model		1.37	1.03 - 1.82 (0.03)	61.5	0.02	- 0.19	0.85	1.37	0.24
	Recessive model		0.93	0.70 - 1.24 (0.62)	28.2	0.22	1.32	0.18	2.02	0.07
	Allelic model	1575 / 3658	1.28	0.99 - 1.65 (0.05)	72.9	< 0.001	1.32	0.18	2.30	0.08
	TT *vs* CC		1.06	0.72 - 1.57 (0.75)	31.2	0.20	2.07	0.03	3.04	0.04
	TC *vs* CC		1.33	1.03 - 1.72 (0.03)	48.9	0.08	- 0.94	0.34	1.13	0.32
Mixed	Dominant model		1.01	0.82 - 1.24 (0.90)	10.1	0.35	- 0.21	0.83	0.70	0.50
	Recessive model		0.94	0.79 - 1.11 (0.46)	18.5	0.27	2.71	0.002	5.21	0.001
	Allelic model	1996 / 2112	1.01	0.87 - 1.18 (0.85)	39.6	0.10	1.88	0.06	2.44	0.04
	TT *vs* CC		0.99	0.75 - 1.32 (0.97)	34.9	0.13	0.21	0.83	1.44	0.19

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
	TC *vs* CC		0.98	0.81 - 1.19 (0.86)	0	0.65	- 0.42	0.67	0.66	0.53
East-Asian	Dominant model		0.92	0.73 - 1.14 (0.44)	77.6	< 0.001	0.08	0.93	- 0.40	0.69
	Recessive model		0.82	0.72 - 0.93 (< 0.001)	25.7	0.19	1.32	0.18	2.02	0.07
	Allelic model	4859 / 5856	0.94	0.79 - 1.12 (0.48)	79.9	< 0.001	- 0.08	0.93	0.81	0.43
	TT *vs* CC		0.79	0.65 - 0.95 (0.01)	55.6	0.01	1.17	0.24	1.37	0.20
	TC *vs* CC		0.93	0.75 - 1.14 (0.48)	72	< 0.001	- 0.08	0.93	- 0.35	0.73
South-Asian	Dominant model		2.12	0.95 - 4.73 (0.06)	80.5	0.02	1	0.31	-	-
	Recessive model		0.72	0.47 - 1.08 (0.11)	0	0.33	1	0.31	-	-
	Allelic model	395 / 395	1.50	0.72 - 3.12 (0.28)	86	< 0.001	1	0.31	-	-
	TT *vs* CC		0.99	0.64 - 1.53 (0.95)	7	0.30	1	0.31	-	-
	TC *vs* CC		2.91	1.17 - 7.21 (0.02)	77	0.03	1	0.31	-	-

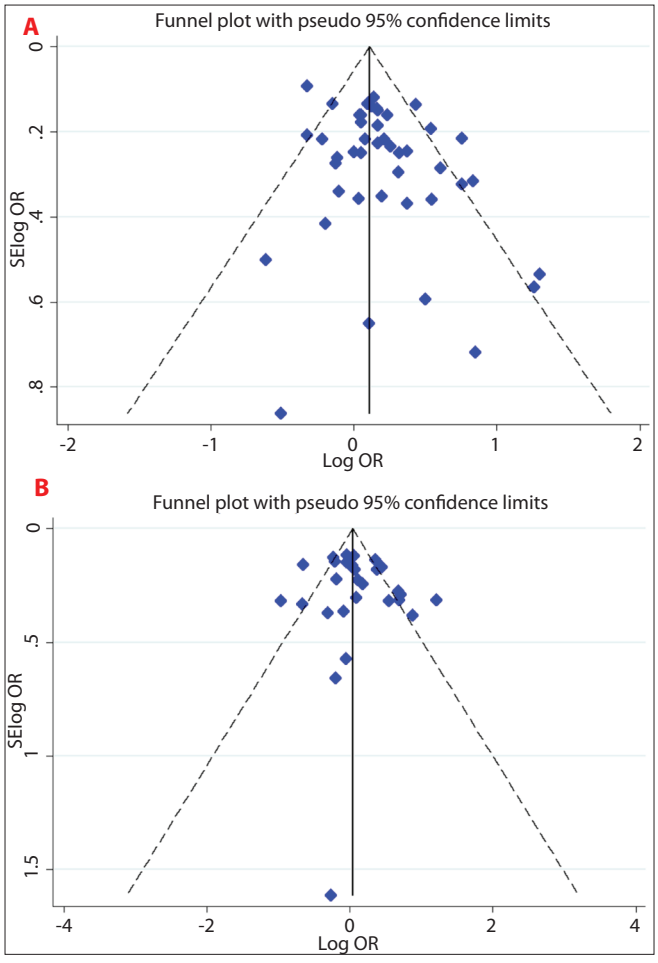


Figure 4 *- Begg's funnel plot for publication bias test in overall analysis. Each point represents a separate study for the indicated association. A: Dominant model (rs20541); B: Dominant model (rs1800925).*

Meta-analysis confers an appropriate technique to solve the issue of inconsistency through tackling the limitation of insufficient statistical power and small sample size present in the individual studies. As a consequence, in order to come up with a solution for the mentioned limitations with respect to *IL13* gene polymorphisms, the current most up-to-date meta-analysis was carried oud, in order to achieve a bona fide estimation of the association between *IL13* gene rs20541 and rs1800925 polymorphisms and the risk of asthma. Asthma is a chronic inflammatory disorder of the airways. The disease has been attributed with hyperactivity of Th2 responses of the immune system, in which the cytokines of the type 2 immunity, including IL-4, IL-5, and IL-13 promotes harmful events in the airways. IL-13 has been demonstrated to cause differentiation of goblet cells, bronchial hyperresponsiveness, fibroblast activation, and isotype switching of B cell antibody production to IgE (73). Targeting IL-13 in clinical trials has revealed an amelioration in the clinical presentations of asthma, suggesting the role of IL-13 in the pathogenesis of asthma (74). In addition, exogenous administration of IL-13 into airways in the animal models was shown to establish an inflammatory state by enhanced infiltration of eosinophils, and exacerbation of asthmatic responses, such airway hyperresponsiveness and contraction of the airway muscle (75). Moreover, blocking the IL-13 suppress the production of mucus (76).

Among the genes associated with asthma risk, *IL13* gene polymorphisms have been vastly surveyed. Functionally, *IL13* gene – 1112C/T (rs1800925) polymorphism was associated with upregulation IL-13 mRNA expression in the polarized Th2 cells as well as promoted release of this cytokine by mitogen-stimulated mononuclear cells (77). Additionally, the AA genotype of the *IL13* gene + 2044A/G (rs20541) polymorphism was reported to upregulate the IL-13 mRNA expression and reduce the affinity of IL-13 for binding to IL-13 receptor (78). As a result, these two SNPs in the *IL13* gene are involved in modulation of the cytokine level and contribution to the pathogenesis of asthma.

Figure 5 *- Sensitivity analysis in present meta-analysis investigates the individual influence of studies on pooled results. A: Dominant model (rs20541); B: Dominant model (rs1800925).*

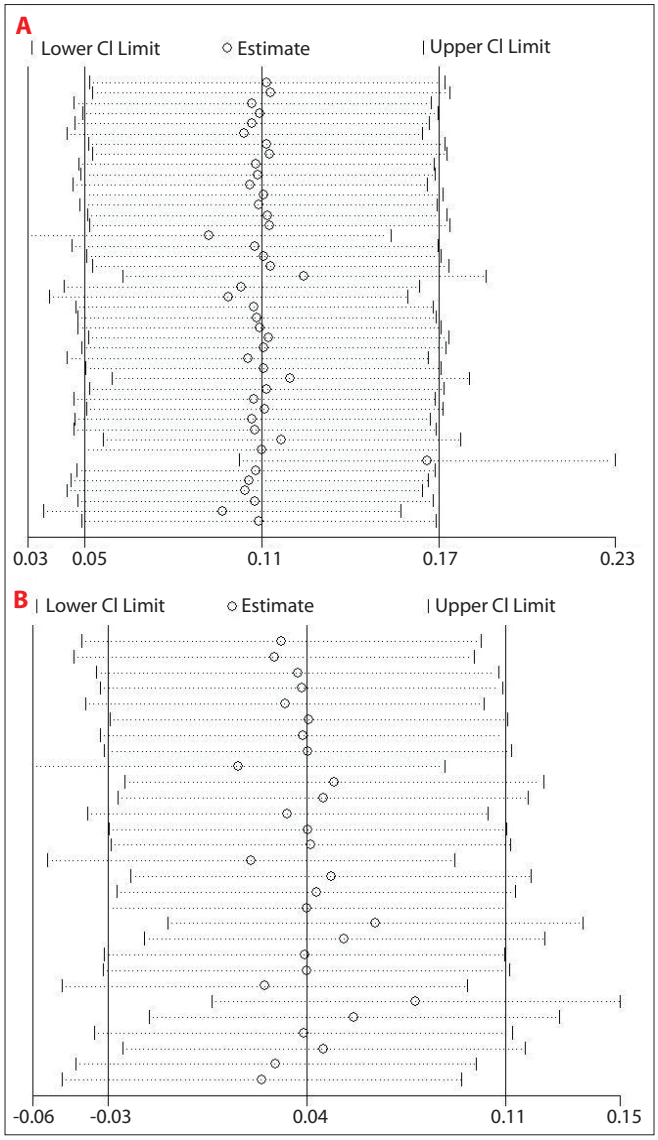
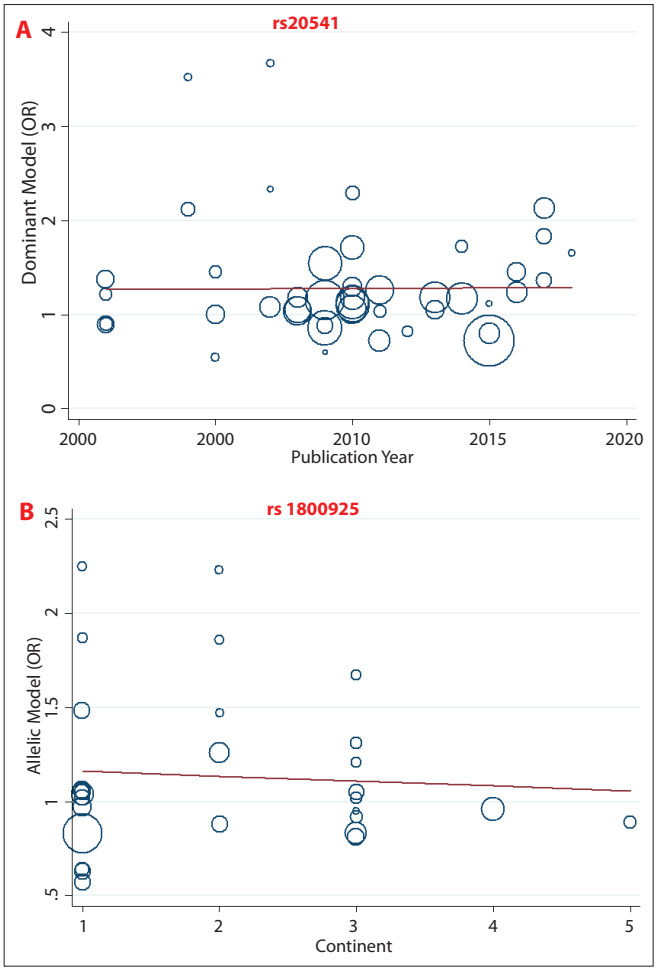


Figure 6 *- Meta-regression plots of the association between IL-13 gene polymorphism and risk of asthma. A: Dominant model based on publication year (rs20541); B: Allelic model based on continent (rs1800925).*



The latest meta-analysis by Mei *et al.* in 2017, by including 25 case-control studies, indicated that rs20541 polymorphism was associated in the overall analysis (OR = 1.49, 95% CI = 1.11-2.01) as well as in the Asian population in children (OR = 1.59, 95% CI = 1.05-2.40) (79). However, in the current meta-analysis, 45 case-control studies for rs20541 polymorphism, containing 10572 cases and 11575 healthy controls, were included. At the moment, this is the largest and most comprehensive meta-analysis of the *IL13* gene rs20541 polymorphism and asthma risk that considerably improved the sample size in comparison to the previous meta-analysis studies. In the pooled analysis, we observed than all of the genetic comparisons, including dominant (OR = 1.18), recessive (OR = 1.14), allelic (OR = 1.16), AA *vs* GG (OR = 1.17), and GA *vs* GG (OR = 1.14) models increased the susceptibility of asthma. In the subgroup analysis, it was detected that rs20541 polymorphism was not significantly associated with asthma risk in American population, while dominant (OR = 1.28), allelic (OR = 1.17), and GA *vs* GG (OR = 1.33) models increased asthma risk in Europeans. Additionally, except the heterozygote model, a strong significant association between rs20541 polymorphism and asthma risk in Asian population was detected. Additionally, the meta-analysis performed in 2011 (80) indicated that the allelic model of rs20541 was associated with an increased risk of asthma in Asians (OR 1.436, 95% CI = 1.101-1.873). To attain more precise conclusion, we per-

Table IV *- Meta-regression analyses of potential source of heterogeneity.*

Heterogeneity Factor		Coefficient	SE	T	P-value	95% CI	
IL13 **(rs20541)**						**UL**	**LL**
Publication Year	Dominant model	0.0011	0.018	0.06	0.95	- 0.035	0.037
	Recessive model	0.046	0.0270	1.72	0.093	- 0.0080	0.1012
	Allelic model	0.157	0.0134	1.17	0.24	- 0.0113	0.0427
	AA *vs* GG	0.0150	0.031	0.47	0.63	- 0.0489	0.0789
	GA *vs* GG	- 0.006	0.018	- 0.35	0.72	- 0.043	0.030
Continent	Dominant model	- 0.096	0.077	- 1.25	0.21	- 0.252	0.059
	Recessive model	- 0.128	0.122	- 1.05	0.299	- 0.375	0.118
	Allelic model	- 0.089	0.0580	- 1.55	0.13	- 0.206	0.027
	AA *vs* GG	- 0.180	0.136	- 1.32	0.19	- 0.456	0.095
	GA *vs* GG	- 0.056	0.076	- 0.73	0.46	- 0.211	0.098
Genotyping Methods	Dominant model	- 0.145	0.096	- 1.50	0.14	- 0.340	0.049
	Recessive model	0.002	0.151	0.02	0.98	- 0.302	0.307
	Allelic model	- 0.082	0.073	- 1.12	0.27	- 0.230	0.066
	AA *vs* GG	- 0.155	0.169	- 0.91	0.36	- 0.497	0.187
	GA *vs* GG	- 0.118	0.096	- 1.22	0.22	- 0.313	0.076
IL13 **(rs1800925)**							
Publication Year	Dominant model	- 0.016	0.028	- 0.58	0.56	- 0.074	0.041
	Recessive model	- 0.128	0.046	- 2.78	0.11	- 0.222	0.033
	Allelic model	- 0.030	0.019	- 1.58	0.12	- 0.070	0.009
	TT *vs* CC	- 0.190	0.058	- 3.24	0.23	- 0.311	0.069
	TC *vs* CC	0.020	0.036	0.55	0.58	- 0.055	0.095
Continent	Dominant model	- 0.058	0.104	- 0.56	0.58	- 0.272	0.156
	Recessive model	0.032	0.177	0.19	0.85	- 0.330	0.396
	Allelic model	- 0.026	0.072	- 0.37	0.71	- 0.174	0.121
	TT *vs* CC	0.031	0.251	0.13	0.90	- 0.485	0.548
	TC *vs* CC	- 0.118	0.136	- 0.87	0.39	- 0.397	0.160
Genotyping Methods	Dominant model	- 0.245	0.147	- 1.67	0.10	- 0.547	0.056
	Recessive model	0.084	0.267	0.32	0.75	- 0.465	0.634
	Allelic model	- 0.092	0.106	- 0.88	0.38	- 0.310	0.124
	TT *vs* CC	- 0.018	0.374	- 0.05	0.96	- 0.786	0.749
	TC *vs* CC	- 0.371	0.189	- 1.96	0.06	- 0.759	0.016

formed subgroup analysis based on the genetic stratification of the study subjects. It was divulged that rs20541 polymorphism was not a genetic risk factor for asthma in subjects with mixed ethnicity (mostly composed of Caucasians, Latins, and American-Africans). In addition, dominant, allelic and heterozygote models of rs20541 polymorphism were associated with asthma risk in Caucasians. Ultimately, we categorized Asian populations to East-Asian, South-Asian and Middle-East populations. Interestingly, significant associations were observed between rs20541 polymorphism and asthma risk in the South-Asian and Middle-East populations, but no significant association was observed in East-Asians. Interestingly, meta-regression analysis revealed that publication year, continent of the included patients and genotyping method were not source of heterogenicity in evaluating rs20541 polymorphism. Nonetheless, the diversity in the study design as well as genetic background of the populations between the different races/ethnicities/countries might be the possible reason for inconsistent results among the different populations.

The previous meta-analysis of *IL13* gene rs1800925 polymorphism in 2013, by including 22 studies (containing 5834 cases and 8110 controls), indicated that the dominant genetic model increased the risk of asthma (OR = 1.20, 95% CI = 1.08-1.34). Moreover, rs1800925 polymorphism was associated with increased asthma risk in Caucasians (OR = 1.30, 95% CI 1.09-1.55), but no significant association was found in Asians and African Americans (81). In addition, the meta-analysis in 2011 indicated that rs1800925 polymorphism was not associated with asthma risk in Asians (80). In the current meta-analysis, on the other hand, 31 studies, containing 10139 cases and 13304 healthy controls for rs1800925 polymorphisms were retrieved. The results of overall pooled analysis revealed no significant association between *IL13* gene rs1800925 polymorphism and asthma risk under different genotype models except for recessive model (OR = 0.86), which decreased asthma risk. In the subgroup analysis, it was revealed that rs1800925 was not significantly associated with the risk of asthma in Americans. Nonetheless, dominant (OR = 1.52), allelic (OR = 1.40), and CT *vs* CC (OR = 1.51) models were associated with increased susceptibility to asthma in the European populations. Furthermore, recessive and homozygote models decreased the risk of asthma in the Asians. Additionally, subgroup analysis based on the ethnicity-specific stratification supported the positive association of rs1800925 and asthma risk in Caucasians (dominant and TC *vs* CC) and South-Asian (just in TC *vs* CC). However, this association was negative in East-Asian (dominant and TT *vs* CC model). Based on the meta-regression analysis, it was found that publication year, continent of the included patients and genotyping method were not source of heterogenicity for rs1800925 polymorphism.

There are some limitations and caveats that needs to be mentioned. First, the analysis was performed according to crude estimation of *IL13* gene association with asthma susceptibility, regardless of the impression of confounders, such as age of the patients, age of diagnosis/time of follow-up, sex, smoking, asthma severity, and contribution of other genes in LD with *IL13*. Additionally, studies with diagnosis of atopy were excluded as this might be messed up with diagnosis of asthma. Second, we did not analyze several genes that could be helpful to understand the cytokine contribution in the pathogenesis of asthma. Third, there was a degree of heterogeneity during the overall analysis. From statistical perspective, this heterogeneity describes the variability between included studies and may originate from clinical or methodological heterogeneity, other unreported or unknown study characteristics, or by chance. Therefore, for finding any sources of heterogeneity and attenuating their effects, we conducted subgroup analysis and weighted meta-regression. Collectively, the results of meta-regression showed that none of the parameters, including publication year, continent of the study population, and genotyping methods were the expected source of heterogeneity. However, subgroup analysis was associated with a reduced heterogeneity in all groups and explained part of the observed heterogeneity. Furthermore, the other way of dealing with statistical heterogeneity performed in our analysis, was to incorporate "Random" term to account for it in a random-effects. Random effect model typically produces more conservative estimates of the significance of a result (a wider confidence interval). As it gives proportionately higher weights to smaller studies and lower weights to larger studies compared to the fixed effect analysis. Fourth, in the subgroup analysis, there was small sample size of many groups, leading to underpowered subgroup analyses. Moreover, there might be possible false-negative associations in the subgroup analysis due to unclarity of the actual number of cases/controls for each genetic model as well as no power assessment by each study. Fifth, this study was solely focused on the articles published in the English language which can be potential source of bias.

Conclusions

Considering all the facts, we performed the most up-to-date analysis of the *IL13* gene rs20541 and rs1800925 polymorphisms and asthma risk before September 2020. Our meta-analysis further validated some results of the last meta-analysis, while rejected some of them. In a whole insight, rs20541 polymorphism was detected as a potential risk factor for asthma in overall analysis, Asians (all models except GA *vs* GG), Europeans (all models except recessive and AA *vs* GG), Caucasians (all models except recessive and AA *vs* GG), East-Asians (just allelic model), Middle-East (all models except recessive and AA *vs* GG), and South-East (just in recessive and allelic models). Additionally, rs1800925 polymorphism showed statistically significant associated with asthma in the overall analysis (just in recessive model), Asians (in recessive and TT *vs* CC models), Europeans (all models except recessive and TT *vs* CC), Caucasians (just in dominant and TC *vs* CC), East-Asian (in dominant and TT *vs* CC model) and South-Asian (just in TC *vs* CC). Although previous met-analysis studies on small sample size indicated primitive associations of the IL13 gene polymorphisms with asthma susceptibility and regarding that our analysis large-

ly improved this limitation, we encourage further comprehensive analysis in the future after yielding more original data, particularly with respect to the role of IL13 polymorphisms in association with clinical presentations of asthmatic patients.

Contributors

MO, DI: originated the study and acquired data. BR, MM: performed statistical analysis, interpreted data and drafted the manuscript. SA, SF: revised the manuscript. All the authors read and approved the final version of the manuscript.

Fundings

None.

Acknowledgements

We would like to thanks Omid Dehghan (beshkaneh) for all her support.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J. 2014;7(1):12. doi: 10.1186/1939-4551-7-12.
2. Makoui MH, Imani D, Motallebnezhad M, Azimi M, Razi B. Vitamin D receptor gene polymorphism and susceptibility to asthma: Meta-analysis based on 17 case-control studies. Ann Allergy Asthma Immunol. 2020;124(1):57-69. doi: 10.1016/j.anai.2019.10.014.
3. Willemsen G, van Beijsterveldt TC, van Baal CG, Postma D, Boomsma DI. Heritability of self-reported asthma and allergy: a study in adult Dutch twins, siblings and parents. Twin Res Hum Genet. 2008;11(2):132-42. doi: 10.1375/twin.11.2.132.
4. Thomsen SF, van der Sluis S, Kyvik KO, Skytthe A, Backer V. Estimates of asthma heritability in a large twin sample. Clin Exp Allergy. 2010;40(7):1054-61. doi: 10.1111/j.1365-2222.2010.03525.x.
5. Bierbaum S, Heinzmann A. The genetics of bronchial asthma in children. Respir Med. 2007;101(7):1369-75. doi: 10.1016/j.rmed.2007.01.018.
6. Wu AY, Sur S, Grant JA, Tripple JW. Interleukin-4/interleukin-13 versus interleukin-5: a comparison of molecular targets in biologic therapy for the treatment of severe asthma. Curr Opin Allergy Clin Immunol. 2019;19(1):30-7. doi: 10.1097/aci.0000000000000490.
7. Corren J. Role of interleukin-13 in asthma. Curr Allergy Asthma Rep. 2013;13(5):415-20. doi: 10.1007/s11882-013-0373-9
8. Tomkinson A, Duez C, Cieslewicz G, Pratt JC, Joetham A, Shanafelt MC, Gundel R, Gelfand EW. A murine IL-4 receptor antagonist that inhibits IL-4- and IL-13-induced responses prevents antigen-induced airway eosinophilia and airway hyperresponsiveness. J Immunol. 2001;166(9):5792-800. doi: 10.4049/jimmunol.166.9.5792.
9. Barnes PJ. Pathophysiology of allergic inflammation. Immunol Rev. 2011;242(1):31-50. doi: 10.1111/j.1600-065X.2011.01020.x.
10. Walter DM, McIntire JJ, Berry G, McKenzie AN, Donaldson DD, DeKruyff RH, *et al*. Critical role for IL-13 in the development of allergen-induced airway hyperreactivity. J Immunol. 2001 Oct 15;167(8):4668-75. doi: 10.4049/jimmunol.167.8.4668.
11. Huang SK, Xiao HQ, Kleine-Tebbe J, Paciotti G, Marsh DG, Lichtenstein LM, *et al*. IL-13 expression at the sites of allergen challenge in patients with asthma. J Immunol. 1995;155(5):2688-94. Available at: https://pubmed.ncbi.nlm.nih.gov/7650396/.
12. Frazer KA, Ueda Y, Zhu Y, Gifford VR, Garofalo MR, Mohandas N, *et al.* Computational and biological analysis of 680 kb of DNA sequence from the human 5q31 cytokine gene cluster region. Genome Res. 1997;7(5):495-512. doi: 10.1101/gr.7.5.495.
13. Cui L, Jia J, Ma CF, Li SY, Wang YP, Guo XM, *et al*. IL-13 polymorphisms contribute to the risk of asthma: a meta-analysis. Clin Biochem. 2012;45(4-5):285-8. doi: 10.1016/j.clinbiochem.2011.12.012.
14. Chen W, Ericksen MB, Levin LS, Khurana Hershey GK. Functional effect of the R110Q IL13 genetic variant alone and in combination with IL4RA genetic variants. J Allergy Clin Immunol. 2004;114(3):553-60. doi: 10.1016/j.jaci.2004.04.044.
15. Vladich FD, Brazille SM, Stern D, Peck ML, Ghittoni R, Vercelli D. IL-13 R130Q, a common variant associated with allergy and asthma, enhances effector mechanisms essential for human allergic inflammation. J Clin Invest. 2005;115(3):747-54. doi: 10.1172/JCI22818.
16. Graves PE, Kabesch M, Halonen M, Holberg CJ, Baldini M, Fritzsch C, *et al*. A cluster of seven tightly linked polymorphisms in the IL-13 gene is associated with total serum IgE levels in three populations of white children. J Allergy Clin Immunol. 2000;105(3):506-13. doi: 10.1067/mai.2000.104940.
17. Vercelli D. Genetics of IL-13 and functional relevance of IL-13 variants. Curr Opin Allergy Clin Immunol. 2002;2(5):389-93. doi: 10.1097/00130832-200210000-00004.
18. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, W64. doi: 10.7326/0003-4819-151-4-200908180-00135.
19. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5. doi: 10.1007/s10654-010-9491-z.
20. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods. 2006;11(2):193-206. doi: 10.1037/1082-989X.11.2.193.
21. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-48. Available at: https://pubmed.ncbi.nlm.nih.gov/13655060/.
22. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34. doi: 10.1136/bmj.315.7109.629.
23. Hakonarson H, Bjornsdottir US, Ostermann E, Arnason T, Adalsteinsdottir AE, Halapi E, *et al*. Allelic frequencies and patterns of single-nucleotide polymorphisms in candidate genes for asthma and atopy in Iceland. Am J Respir Crit Care Med. 2001;164(11):2036-44. doi: 10.1164/ajrccm.164.11.2101086.
24. Howard TD, Whittaker PA, Zaiman AL, Koppelman GH, Xu J, Hanley MT, *et al*. Identification and association of polymorphisms in the interleukin-13 gene with asthma and atopy in a Dutch population. Am J Respir Cell Mol Biol. 2001;25(3):377-84. doi: 10.1165/ajrcmb.25.3.4483.
25. Kauppi P, Lindblad-Toh K, Sevon P, Toivonen HT, Rioux JD, Villapakkam A, *et al*. A second-generation association study of the 5q31

cytokine gene cluster and the interleukin-4 receptor in asthma. Genomics. 2001;77(1-2):35-42. doi: 10.1006/geno.2001.6613.
26. Leung TF, Tang NL, Chan IH, Li AM, Ha G, Lam CW. A polymorphism in the coding region of interleukin-13 gene is associated with atopy but not asthma in Chinese children. Clin Exp Allergy. 2001;31(10):1515-21. doi: 10.1046/j.1365-2222.2001.01212.x.
27. Xi D, Pan S, Cui T, Wu J. Association between IL-13 gene polymorphism and asthma in Han nationality in Hubei Chinese population. J Huazhong Univ Sci Technolog Med Sci. 2004;24(3):219-22. doi: 10.1007/BF02831994.
28. Liu J WB, Chen H. Relationships among IL-13 gene polymorphism, asthma and plasma cytokine levels. J Clin Pulm Med 2004:122-4. Available at: https://en.cnki.com.cn/Article_en/CJFDTOTAL-LCFK200402013.htm.
29. Donfack J, Schneider DH, Tan Z, Kurz T, Dubchak I, Frazer KA, *et al*. Variation in conserved non-coding sequences on chromosome 5q and susceptibility to asthma and atopy. Respir Res. 2005;6(1):145. doi: 10.1186/1465-9921-6-145.
30. Kaishu Z, Jirong L, Shanyu L, *et al.* Correlationship between interleukin-13 genotype and phenotype in children with bronchial asthma. J Clin Pediatr 2005:312-14.
31. Bernstein DI, Wang N, Campo P, Chakraborty R, Smith A, Cartier A, *et al*. Diisocyanate asthma and gene-environment interactions with IL4RA, CD-14, and IL-13 genes. Ann Allergy Asthma Immunol. 2006;97(6):800-6. doi: 10.1016/S1081-1206(10)60972-6.
32. Hosseini-Farahabadi S, Tavakkol-Afshari J, Rafatpanah H, Farid Hosseini R, Khaje Daluei M. Association between the polymorphisms of IL-4 gene promoter (-590C>T), IL-13 coding region (R130Q) and IL-16 gene promoter (-295T>C) and allergic asthma. Iran J Allergy Asthma Immunol. 2007;6(1):9-14. Available at: https://pubmed.ncbi.nlm.nih.gov/17303923/.
33. Battle NC, Choudhry S, Tsai HJ, Eng C, Kumar G, Beckman KB, *et al.* Ethnicity-specific gene-gene interaction between IL-13 and IL-4Ralpha among African Americans with asthma. Am J Respir Crit Care Med. 2007;175(9):881-7. doi: 10.1164/rccm.200607-992OC.
34. Chan IH, Tang NL, Leung TF, Huang W, Lam YY, Li CY, *et al*. Study of gene-gene interactions for endophenotypic quantitative traits in Chinese asthmatic children. Allergy. 2008 Aug;63(8):1031-9. doi: 10.1111/j.1398-9995.2008.01639.x.
35. Kang MJ, Lee SY, Kim HB, Yu J, Kim BJ, Choi WA, *et al*. Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. Pharmacogenet Genomics. 2008;18(7):551-8. doi: 10.1097/FPC.0b013e3282fe94c5.
36. Kim HB, Kang MJ, Lee SY, Jin HS, Kim JH, Kim BS, *et al*. Combined effect of tumour necrosis factor-alpha and interleukin-13 polymorphisms on bronchial hyperresponsiveness in Korean children with asthma. Clin Exp Allergy. 2008;38(5):774-80. doi: 10.1111/j.1365-2222.2008.02965.x.
37. Black S, Teixeira AS, Loh AX, Vinall L, Holloway JW, Hardy R, *et al*. Contribution of functional variation in the IL13 gene to allergy, hay fever and asthma in the NSHD longitudinal 1946 birth cohort. Allergy. 2009;64(8):1172-8. doi: 10.1111/j.1398-9995.2009.01988.x.
38. Daley D, Lemire M, Akhabir L, Chan-Yeung M, He JQ, McDonald T, *et al*. Analyses of associations with asthma in four asthma population samples from Canada and Australia. Hum Genet. 2009;125(4):445-59. doi: 10.1007/s00439-009-0643-8.
39. Jiang P, Liu J, Yan XB, Liu RY. Several interleukin-4 and interleukin-13 gene single nucleotide polymorphisms among Chinese asthmatic patients. Allergy Asthma Proc. 2009;30(4):413-8. doi: 10.2500/aap.2009.30.3255.
40. Llanes E, Quiralte J, López E, Sastre B, Chacártegui M, del Pozo V, *et al*. Analysis of polymorphisms in olive pollen allergy: IL13, IL4RA, IL5 and ADRB2 genes. Int Arch Allergy Immunol. 2009;148(3):228-38. doi: 10.1159/000161583.
41. Wang JY, Liou YH, Wu YJ, Hsiao YH, Wu LS. An association study of 13 SNPs from seven candidate genes with pediatric asthma and a preliminary study for genetic testing by multiple variants in Taiwanese population. J Clin Immunol. 2009;29(2):205-9. doi: 10.1007/s10875-008-9256-6.
42. Bottema RW, Nolte IM, Howard TD, Koppelman GH, Dubois AE, de Meer G, Kerkhof M, *et al*. Interleukin 13 and interleukin 4 receptor-α polymorphisms in rhinitis and asthma. Int Arch Allergy Immunol. 2010;153(3):259-67. doi: 10.1159/000314366.
43. Wu X, Li Y, Chen Q, Chen F, Cai P, Wang L, *et al*. Association and gene-gene interactions of eight common single-nucleotide polymorphisms with pediatric asthma in middle china. J Asthma. 2010;47(3):238-44. doi: 10.3109/02770900903509099.
44. Yang L, Zhang Y, Liu Q. Genetic Arg144Gln polymorphism of interleukin-13 and asthma in children. Zhong Guo Xian Dai Yi Yao Za Zhi 2010;12(3):46-7.
45. Dmitrieva-Zdorova EV, Voron'ko OE, Aksenova MG, Bodoev NV. [Association of interleukin-13 gene polymorphisms with atopic bronchial asthma]. Genetika. 2010;46(1):111-7. Russian. Available at: https://pubmed.ncbi.nlm.nih.gov/20198887/.
46. Palikhe NS, Kim SH, Cho BY, Choi GS, Kim JH, Ye YM, *et al*. IL-13 Gene Polymorphisms are Associated With Rhinosinusitis and Eosinophilic Inflammation in Aspirin Intolerant Asthma. Allergy Asthma Immunol Res. 2010;2(2):134-40. doi: 10.4168/aair.2010.2.2.134.
47. Undarmaa S, Mashimo Y, Hattori S, Shimojo N, Fujita K, Miyatake A, *et al*. Replication of genetic association studies in asthma and related phenotypes. J Hum Genet. 2010;55(6):342-9. doi: 10.1038/jhg.2010.32.
48. Baye TM, Butsch Kovacic M, Biagini Myers JM, Martin LJ, Lindsey M, Patterson TL, *et al*. Differences in candidate gene association between European ancestry and African American asthmatic children. PLoS One. 2011;6(2):e16522. doi: 10.1371/journal.pone.0016522.
49. Yang XX, Li FX, Wu YS, Wu D, Tan JY, Li M. Association of TGF-beta1, IL-4 and IL-13 gene polymerphisms with asthma in a Chinese population. Asian Pac J Allergy Immunol 2011;29(3):273-7. Available at: https://pubmed.ncbi.nlm.nih.gov/22053598/.
50. Muñoz B, Magaña JJ, Romero-Toledo I, Juárez-Pérez E, López-Moya A, Leyva-García N, *et al*. The relationship among IL-13, GSTP1, and CYP1A1 polymorphisms and environmental tobacco smoke in a population of children with asthma in Northern Mexico. Environ Toxicol Pharmacol. 2012;33(2):226-32. doi: 10.1016/j.etap.2011.12.007.
51. Liu Q, Hua L, Fang D, Lin Q, Zhu Y, Gan X, *et al*. Interleukin-13 and RANTES polymorphisms in relation to asthma in children of Chinese Han nationality. Asian Pac J Allergy Immunol. 2013;31(3):247-52. doi: 10.12932/AP0298.31.3.2013.
52. Shazia M, Kanza M, Mehwish I, Irum S, Farida A, Asifa A. IL-13 gene polymorphisms and their association with atopic asthma and rhinitis in Pakistani patients. Iran J Allergy Asthma Immunol 2013;12(4):391-6. Available at: https://pubmed.ncbi.nlm.nih.gov/23996716/.
53. Berenguer AG, Fernandes AT, Oliveira S, Rodrigues M, Ornelas P, Romeira D, *et al*. Genetic polymorphisms and asthma: findings from a case-control study in the Madeira island population. Biol Res. 2014;47(1):40. doi: 10.1186/0717-6287-47-40.

54. Martínez-Aguilar NE, Del Río-Navarro BE, Navarro-Olivos E, García-Ortíz H, Orozco L, Jiménez-Morales S. SPINK5 and ADRB2 haplotypes are risk factors for asthma in Mexican pediatric patients. J Asthma. 2015;52(3):232-9. doi: 10.3109/02770903.2014.966913.
55. Ramphul K, Hua L, Bao YX, Li JY, Liu QH, Ji RX, *et al*. Identification of IL13 C1923T as a Single Nucleotide Polymorphism for Asthma in Children from Mauritius. Pediatr Allergy Immunol Pulmonol. 2015;28(2):92-5. doi: 10.1089/ped.2014.0464.
56. Davoodi P, Mahesh PA, Holla AD, Ramachandra NB. A preliminary study on the association of single nucleotide polymorphisms of interleukin 4 (IL4), IL13, IL4 receptor alpha (IL4Rα) & Toll-like receptor 4 (TLR4) genes with asthma in Indian adults. Indian J Med Res. 2015;142(6):675-80. doi: 10.4103/0971-5916.174551.
57. Hua L, Zuo XB, Bao YX, Liu QH, Li JY, Lv J, *et al*. Four-locus gene interaction between IL13, IL4, FCER1B, and ADRB2 for asthma in Chinese Han children. Pediatr Pulmonol. 2016;51(4):364-71. doi: 10.1002/ppul.23322.
58. Resende EP, Todo-Bom A, Loureiro C, Mota Pinto A, Oliveiros B, Mesquita L, *et al*. Asthma and rhinitis have different genetic profiles for IL13, IL17A and GSTP1 polymorphisms. Rev Port Pneumol (2006). 2017;23(1):10-6. doi: 10.1016/j.rppnen.2016.06.009.
59. Wan A, Yao B, Zhang X, Li L. Association between interleukin-13 gene polymorphism and neonatal asthma in Han nationality Chinese population. Int J Clin Exp Pathol 2016;9(2):2208-14.
60. Ådjers K, Luukkainen A, Pekkanen J, Hurme M, Huhtala H, Renkonen R, *et al*. Self-Reported Allergic Rhinitis and/or Allergic Conjunctivitis Associate with IL13 rs20541 Polymorphism in Finnish Adult Asthma Patients. Int Arch Allergy Immunol. 2017;172(2):123-8. doi: 10.1159/000456009.
61. Alasandagutti ML, Ansari MS, Sagurthi SR, Valluri V, Gaddam S. Role of IL-13 Genetic Variants in Signalling of Asthma. Inflammation. 2017;40(2):566-77. doi: 10.1007/s10753-016-0503-3.
62. Halwani R, Vazquez-Tello A, Kenana R, Al-Otaibi M, Alhasan KA, Shakoor Z, *et al*. Association of IL-13 rs20541 and rs1295686 variants with symptomatic asthma in a Saudi Arabian population. J Asthma. 2018;55(11):1157-65. doi: 10.1080/02770903.2017.1400047.
63. Zhang JH, Zhang M, Wang YN, Zhang XY. Correlation between IL-4 and IL-13 gene polymorphisms and asthma in Uygur children in Xinjiang. Exp Ther Med. 2019;17(2):1374-82. doi: 10.3892/etm.2018.7096.
64. Ming W, Hongchun S, Shujuan L. Relationship between IL-13 exon 4 gene polymorphisms A2044G and the patients with asthma. Clin Med J China 2007;14:329-30.
65. van der Pouw Kraan TC, van Veen A, Boeije LC, van Tuyl SA, de Groot ER, Stapel SO, *et al*. An IL-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun. 1999;1(1):61-5. doi: 10.1038/sj.gene.6363630.
66. Moissidis I, Chinoy B, Yanamandra K, Napper D, Thurmon T, Bocchini J Jr, *et al*. Association of IL-13, RANTES, and leukotriene C4 synthase gene promoter polymorphisms with asthma and/or atopy in African Americans. Genet Med. 2005;7(6):406-10. doi: 10.1097/01.gim.0000170994.24960.48.
67. DeWan AT, Triche EW, Xu X, Hsu LI, Zhao C, Belanger K, *et al*. PDE11A associations with asthma: results of a genome-wide association scan. J Allergy Clin Immunol. 2010;126(4):871-3.e9. doi: 10.1016/j.jaci.2010.06.051.
68. Noguchi E, Sakamoto H, Hirota T, Ochiai K, Imoto Y, Sakashita M, *et al*. Genome-wide association study identifies HLA-DP as a susceptibility gene for pediatric asthma in Asian populations. PLoS Genet. 2011;7(7):e1002170. doi: 10.1371/journal.pgen.1002170.
69. Dixit P, Awasthi S, Agarwal S. Association of interleukin genes polymorphism with asthma susceptibility in Indian children: a case-control study. Ann Hum Biol. 2015;42(6):552-9. doi: 10.3109/03014460.2014.977347.
70. Li J, Lin LH, Wang J, Peng X, Dai HR, Xiao H, *et al*. Interleukin-4 and interleukin-13 pathway genetics affect disease susceptibility, serum immunoglobulin E levels, and gene expression in asthma. Ann Allergy Asthma Immunol. 2014;113(2):173-9.e1. doi: 10.1016/j.anai.2014.05.004.
71. Li T, Ren Z, Deng Y, Wang Y, Zhou H. Lack of association between RAD50-IL13 polymorphisms and pediatric asthma susceptibility in Northeastern Han Chinese. J Asthma. 2016;53(2):114-8. doi: 10.3109/02770903.2015.1067322.
72. Lilly CM. Diversity of asthma: evolving concepts of pathophysiology and lessons from genetics. J Allergy Clin Immunol. 2005;115(4 Suppl):S526-31. doi: 10.1016/j.jaci.2005.01.028.
73. Voehringer D, Reese TA, Huang X, Shinkai K, Locksley RM. Type 2 immunity is controlled by IL-4/IL-13 expression in hematopoietic non-eosinophil cells of the innate immune system. J Exp Med. 2006;203(6):1435-46. doi: 10.1084/jem.20052448.
74. Davoine F, Cao M, Wu Y, Ajamian F, Ilarraza R, Kokaji AI, *et al*. Virus-induced eosinophil mediator release requires antigen-presenting and CD4+ T cells. J Allergy Clin Immunol. 2008;122(1):69-77, 77.e1-2. doi: 10.1016/j.jaci.2008.03.028.
75. Grünig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, *et al*. Requirement for IL-13 independently of IL-4 in experimental asthma. Science. 1998;282(5397):2261-3. doi: 10.1126/science.282.5397.2261.
76. Blease K, Jakubzick C, Westwick J, Lukacs N, Kunkel SL, Hogaboam CM. Therapeutic effect of IL-13 immunoneutralization during chronic experimental fungal asthma. J Immunol. 2001;166(8):5219-24. doi: 10.4049/jimmunol.166.8.5219.
77. Cameron L, Webster RB, Strempel JM, Kiesler P, Kabesch M, Ramachandran H, *et al*. Th2 cell-selective enhancement of human IL13 transcription by IL13-1112C>T, a polymorphism associated with allergic inflammation. J Immunol. 2006;177(12):8633-42. doi: 10.4049/jimmunol.177.12.8633.
78. Arima K, Umeshita-Suyama R, Sakata Y, Akaiwa M, Mao XQ, Enomoto T, *et al*. Upregulation of IL-13 concentration in vivo by the IL13 variant associated with bronchial asthma. J Allergy Clin Immunol. 2002;109(6):980-7. doi: 10.1067/mai.2002.124656.
79. Mei Q, Qu J. Interleukin-13 +2044 G/A and +1923C/T polymorphisms are associated with asthma susceptibility in Asians: A meta-analysis. Medicine (Baltimore). 2017;96(51):e9203. doi: 10.1097/MD.0000000000009203.
80. Yang H, Dong H, Dai Y, Zheng Y. Association of interleukin-13 C-1112T and G+2044A polymorphisms with asthma: a meta-analysis. Respirology. 2011;16(7):1127-35. doi: 10.1111/j.1440-1843.2011.02021.x.
81. Nie W, Liu Y, Bian J, Li B, Xiu Q. Effects of polymorphisms -1112C/T and +2044A/G in interleukin-13 gene on asthma risk: a meta-analysis. PLoS One. 2013;8(2):e56065. doi: 10.1371/journal.pone.0056065.