



Association between thromboxane A2 receptor polymorphisms and asthma risk: a meta-analysis

Yilin Pan MD, Shaojun Li MD, Xinming Xie PhD & Manxiang Li MD, PhD

To cite this article: Yilin Pan MD, Shaojun Li MD, Xinming Xie PhD & Manxiang Li MD, PhD (2016): Association between thromboxane A2 receptor polymorphisms and asthma risk: a meta-analysis, Journal of Asthma, DOI: [10.3109/02770903.2015.1126849](https://doi.org/10.3109/02770903.2015.1126849)

To link to this article: <http://dx.doi.org/10.3109/02770903.2015.1126849>



Accepted author version posted online: 08 Apr 2016.
Published online: 04 May 2016.



Submit your article to this journal [↗](#)



Article views: 26



View related articles [↗](#)



View Crossmark data [↗](#)

REVIEW

Association between thromboxane A2 receptor polymorphisms and asthma risk: a meta-analysis

Yilin Pan, MD, Shaojun Li, MD, Xinming Xie, PhD, and Manxiang Li, MD, PhD

Department of Respiratory Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

Abstract

Objective: To determine whether there is an association between thromboxane A2 receptor (*TBXA2R*) gene polymorphisms (+924C/T and +795C/T) and asthma risk by conducting a meta-analysis. **Data Sources:** Pubmed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database were searched (updated May 1, 2015). **Study Selections:** Articles evaluating the association between *TBXA2R* gene polymorphisms and asthma risk were selected. **Results:** A total of 7 studies on +924C/T polymorphism and 6 studies on +795C/T polymorphism were included in this meta-analysis. There was a significant association between *TBXA2R* +924C/T polymorphism and asthma risk in the recessive model (OR = 1.33, 95% CI = 1.01–1.75, $P = 0.045$). No significant association between +795C/T polymorphism and asthma risk in the overall population was demonstrated. In subgroup analyzes, significant association was observed in atopic asthma risk in the recessive model (OR = 1.43, 95% CI = 1.01–2.01, $P = 0.043$), but no significant association was found between *TBXA2R* +924C/T polymorphism and asthma risk in Asians (OR = 1.14, 95% CI = 0.80–1.63, $P = 0.457$). *TBXA2R* +795C/T polymorphism was associated with aspirin-intolerant asthma (AIA) risk when stratified by asthma subphenotype in the allelic model (OR = 1.30, 95% CI = 1.05–1.60, $P = 0.014$) and dominant model (OR = 1.50, 95% CI = 1.11–2.03, $P = 0.008$). **Conclusion:** Our results suggested that *TBXA2R* +924C/T polymorphism is associated with asthma risk, and +795C/T polymorphism may be a risk factor for AIA. Larger-scale and well-designed studies are required to validate the association identified in the current meta-analysis.

Keywords

Asthma, thromboxane A2 receptor, meta-analysis, genetic, polymorphism

History

Received 20 August 2015

Revised 31 October 2015

Accepted 27 November 2015

Introduction

Asthma is a chronic inflammatory airway disease characterized by airway hyperresponsiveness and reversible airflow obstruction. This disease occurs with high prevalence worldwide and represents a substantial public health burden in many countries [1]. Thus ascertainment of the causes of asthma has attracted great attention. Although the exact etiology of asthma remains unknown, multiple genetic and environmental elements and their interactions have been detected [2–5], including the gene encoding thromboxane A2 receptor (*TBXA2R*).

Thromboxane A2 (*TXA2*) plays an important role in allergic inflammation and asthma. It exerts its biological functions by binding to its receptor, namely *TBXA2R*. *TBXA2R* is expressed richly in tissues/organs targeted by *TXA2*, including bronchial and vascular smooth muscle, epithelium, endothelium, uterus and placental tissue, thymus, liver and small intestine [6]. Interaction of *TBXA2R* with its ligand can induce acetylcholine release and airway microvascular leakage that are relevant to allergic reaction of asthma [7]. In addition, *TBXA2R*-deficient mice have lower degree of inflammation, cytokine generation

and airway reactivity to wild type levels [8]. Several studies showed that activation of *TBXA2R* in airway smooth muscle cells (ASMCs) would lead to ASMCs contraction, proliferation and hypertrophy [9–11], which occurs in response to airway inflammation in asthma. Furthermore, *TBXA2R* antagonist could reduce lung inflammation, airway hyperresponsiveness and ASMCs hyperplasia in animal models of asthma [12–14]. All these findings indicate that *TBXA2R* might play an important role in the pathogenesis of asthma.

TBXA2R gene is located at 19p13.3, containing 4 exons with total length of 15 kb and encoding a member of the G protein-coupled receptor family [15]. Several studies have investigated the associations between *TBXA2R* polymorphisms and susceptibility to asthma. Most of them focused on two polymorphisms: T924C (*rs4523*), a T to C transition at position +924, and T795C (*rs1131882*), a T to C transition at position +795. These two polymorphisms were thought to affect mRNA stability and the efficiency of receptor transcription or translation, and result in change in transcriptional factor binding sites, leading to altered product levels [16–18]. Previous studies for these polymorphisms, however, are controversial and inconclusive. A single study with a small sample size may not have sufficient power to draw a reliable conclusion, therefore, we performed a meta-analysis to evaluate the association between *TBXA2R* polymorphisms (+924C/T and +795C/T) and asthma risk.

Correspondence: Manxiang Li, MD, PhD, Department of Respiratory Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, No. 277, Yanta West Road, Xi'an, Shaanxi, China. Phone: +86-029-85323855. Fax: +86-029-85323855. E-mail: manxiangli@hotmail.com

Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Identification of eligible studies

Two independent investigators (Pan and Xie) carried out a systematic search in PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) and Wanfang database, with the last search update before May 1, 2015. The following terms were used: “thromboxane A2 receptor OR *TBXA2R*,” “asthma OR asthmatic” and “polymorphism* OR mutation OR variant.” The reference lists of retrieved studies and recent reviews were also manually searched for further relevant studies.

Inclusion and exclusion criteria

Studies in this meta-analysis must meet the following inclusion criteria: (1) case-control study; (2) evaluation of the association between *TBXA2R* +924C/T and (or) +795C/T polymorphisms and asthma risk; (3) genotype distributions in comparison groups should be available for estimating an odds ratios (ORs) with 95% confidence intervals (CIs). Accordingly, the exclusion criteria were as follows: (1) no control population; (2) no available genotype frequency; (3) duplication of the previous publications, the largest or most recent publication was selected; (4) family-based studies of pedigrees; (5) genotype distributions in the control population are not in Hardy-Weinberg equilibrium (HWE). Study selection was achieved by two investigators (Pan and Xie) independently, and all the disagreements were resolved by discussion.

Qualitative assessment

The qualities of the included studies were assessed by two investigators (Pan and Xie), respectively, according to the Newcastle-Ottawa Scale (NOS), which scored studies by the selection of study groups, the comparability of the groups and the exposure of study [19]. We considered a study awarded 0–3, 4–6, or 7–9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion.

Data extraction

Data was extracted from all eligible publications by two investigators (Pan and Xie) independently. The following data were extracted from each study: first author, publication year, original country, ethnicity, age group, atopic status, sample size, genotype numbers of cases and controls. We verified the accuracy of the data by comparing collection forms between investigators. If different results were generated, we would recheck the original data of the included studies and have a discussion to reach consensus.

Statistical analysis

The strength of association between *TBXA2R* polymorphisms and asthma risk were assessed by OR with 95% CI. HWE was evaluated for each study by Chi-square test in control

groups, and $P < 0.05$ was considered a significant departure from HWE. Pooled ORs were performed for allelic comparison (+924C/T: C vs T, +795C/T: C vs T), dominant model (+924C/T: CC + TC vs TT, +795C/T: CC + TC vs TT) and recessive model (+924C/T: CC vs TC + TT, +795C/T: CC vs TC + TT), respectively. The statistical significant level was determined by Z-test with p values less than 0.05. Heterogeneity was calculated using Q statistic (significance level of $P < 0.1$) and I^2 statistic (greater than 50% as evidence of significant inconsistency). Either fixed-effect or random effects model was used to pool the effect sizes according to the heterogeneity. Subgroup analysis was stratified by ethnicity, age, atopic status and asthma subphenotype. Besides, sensitivity analysis was conducted by altering the statistical models (fixed-effect model or random-effect model) to identify the potential influence of different statistical model set on the pooled ORs. Publication bias was assessed through Begg's funnel plot and Egger's linear regression test, and $P < 0.05$ was considered significant. If publication bias existed, the Duval and Tweedie nonparametric “trim and fill” method was performed to further assess the possible effect of publication bias. All statistical analyses were conducted using Stata 12.0 software (Stata Corp, College Station, TX). All p values were two-sided.

Results

Characteristics of eligible studies

As showed in Figure 1, after a comprehensive literature search applying our inclusion and exclusion criteria, 9 [20–28] relevant studies were identified in the final analysis. There were 7 studies of +924C/T polymorphism and 6 studies of +795C/T polymorphism. Of the 7 eligible studies pertinent to +924 C/T polymorphisms, 6 were conducted in Asian populations. For the 6 studies of +795C/T polymorphism, all were conducted in Asians. All studies were assessed by NOS and the score of them ranged from 7 to 9, suggesting that the methodological quality was acceptable. The main characteristics of studies are summarized in Table 1.

Meta-analysis of *TBXA2R* +924C/T polymorphism and asthma

Seven studies investigated the association between +924C/T polymorphism and asthma risk. The total sample sizes for case and control groups were 2775 and 1669, respectively. Random effects model was used in the allele model due to presence of heterogeneity, and fixed effects model was used in the other genetic models. A significant association was observed in recessive model (CC vs TC + TT: OR = 1.33, 95% CI = 1.01–1.75, $P = 0.045$, Figure 2). No significant association was found in other genetic models (C vs T: OR = 0.98, 95% CI = 0.87–1.10, $P = 0.854$; CC + TC vs TT: OR = 0.89, 95% CI = 0.77–1.03, $P = 0.113$, Table 2).

Next, we conducted subgroup analysis according to ethnicity, and no significant association was identified in Asians (CC vs TC + TT: OR = 1.14, 95% CI = 0.80–1.63, $P = 0.457$, Figure 3). In the subgroup analysis by age, no significant association was found among pediatric asthma either. When stratified based on atopic status, the +924C/T polymorphism

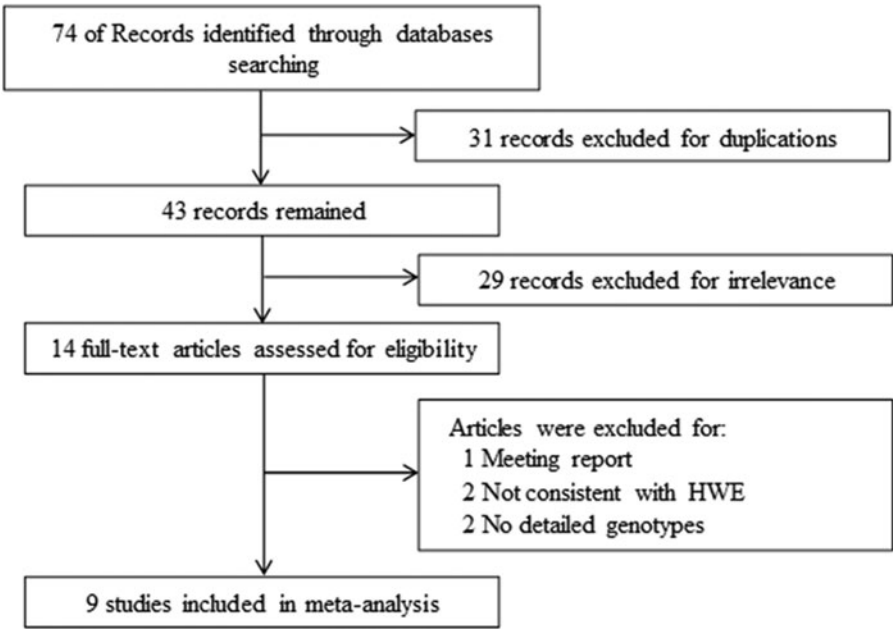


Figure 1. Flow chart of study selection.

was associated with atopic asthma under the recessive model (CC vs $TC + TT$: OR = 1.43, 95% CI = 1.01–2.01, $P = 0.043$, Table 2).

Meta-analysis of TBXA2R +795C/T polymorphism and asthma

Six studies identified an association between +795C/T polymorphism and asthma risk. The total sample sizes for case and control groups were 2568 and 991, respectively. No significant heterogeneity was identified by Q-test and I-squared statistic in any genetic models, thus fixed-effects model was used. The combined results showed that no association was found to be significant in any genetic models (C vs T : OR = 0.97, 95% CI = 0.87–1.09, $P = 0.645$; $CC + TC$ vs TT : OR = 0.97, 95% CI = 0.83–1.14, $P = 0.747$; CC vs $TC + TT$: OR = 0.95, 95% CI = 0.76–1.19, $P = 0.645$, Table 2).

Then, subgroup analysis was conducted according to age. No significant association was identified in adults and children in any genetic models. When stratified based on atopic status, there was no significant association in these three genetic models either. However, in the subgroup analysis by subphenotype, we found a significant association between +795C/T polymorphism and AIA risk under the allelic model (C vs T : OR = 1.30, 95% CI = 1.05–1.60, $P = 0.014$, Figure 4) and dominant model ($CC + TC$ vs TT : OR = 1.50, 95% CI = 1.11–2.03, $P = 0.008$, Table 2).

Sensitivity and publication bias analysis

To assess the reliability of our meta-analysis, we performed a sensitivity analysis by altering the statistical models. The results show that no material alterations were detected. The publication bias estimated by Begg’s funnel plots and

Table 1. Characteristics of studies included in the meta-analysis.

First author						Case			Control			P for HWE	Quality score
						TT	CT	CC	TT	CT	CC		
TBXA2R +924 T>C	Year	Country	Ethnicity	Age group	Atopic status								
Unoki Takeuchi Kim Kim Hong Shin Murk	2000	Japan	Asian	Mixed	NA	425	121	38	204	93	13	0.563	7
	2012	Japan	Asian	Children	Mixed ^a	218	67	5	217	103	8	0.299	9
	2005	Korea	Asian	Adults	Mixed ^a	165	89	11	75	36	7	0.348	8
	2007	Korea	Asian	Children	Mixed ^b	435	227	33	104	48	7	0.629	8
	2005	Korea	Asian	Children	Mixed ^b	197	96	17	67	35	4	0.828	8
	2003	Korea	Asian	Mixed	Mixed ^b	338	169	24	105	52	7	0.861	7
	2011	America	Mixed ^b	Children	Atopic	11	35	54	64	220	200	0.775	7
TBXA2R +795 T>C				TT	CT	CC	TT	CT	CC				
Takeuchi	2012	Japan	Asian	Children	Mixed ^a	116	139	35	139	148	41	0.869	9
Kim	2005	Korea	Asian	Adults	Mixed ^a	102	124	38	40	56	22	0.759	8
Kim	2007	Korea	Asian	Children	Mixed ^b	248	340	107	63	78	18	0.401	8
Shin	2003	Korea	Asian	Mixed	Mixed ^b	217	240	76	58	79	27	0.991	7
Kohyama	2012	Japan	Asian	Adults	Mixed ^a	302	240	54	42	50	8	0.191	7
Kim	2007	Korea	Asian	Adults	Mixed ^a	52	106	32	42	54	26	0.273	8

^aDifferent data could not be extracted separately; ^bDifferent data could be extracted separately; NA, not available; HWE, Hardy–Weinberg equilibrium.

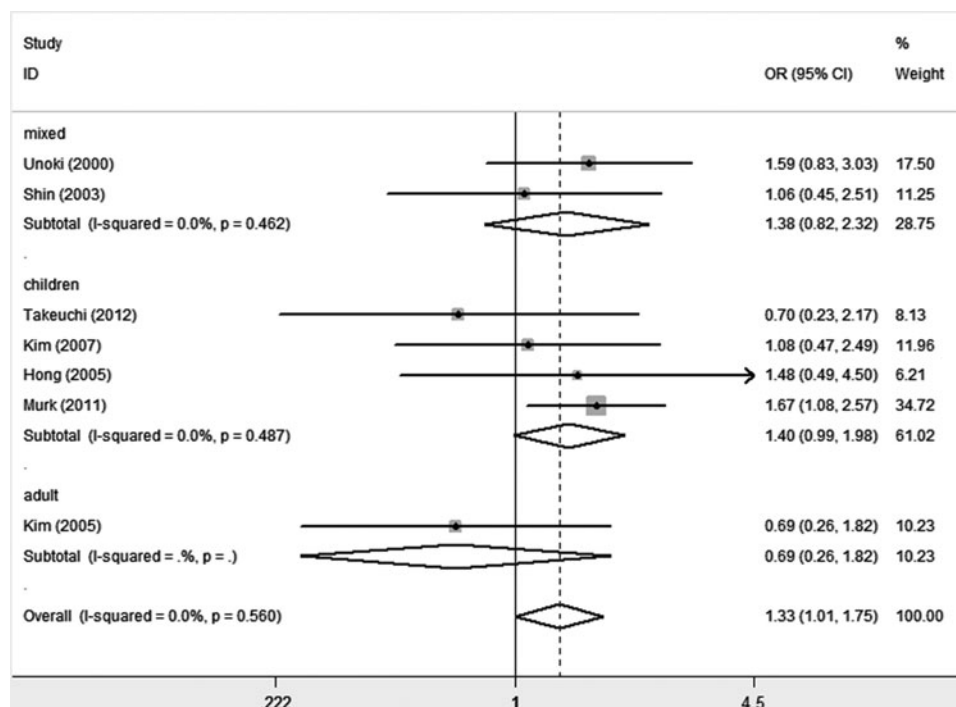


Figure 2. Forest plot of recessive comparison of *TBXA2R* +924C/T (CC vs TC + TT) in fixed effect model.

Egger's linear regression test. The result suggested that publication bias was existed for *TBXA2R* +924C/T in the recessive model (CC vs TC + TT: $P = 0.032$ for Egger's test, Figure 5). Therefore, we performed the trim and fill analysis to further assess the possible effects on results caused by publication bias. The pooled analysis still indicated a significant association between *TBXA2R* +924C/T and asthma risk in the recessive model (CC vs TC + TT: OR = 1.32, 95% CI = 1.004–1.741, $P = 0.047$). No publication bias for the association between *TBXA2R* +795C/T polymorphism and asthma risk was identified by Begg's funnel plot or Egger's regression test.

Discussion

To the best of our knowledge, this is the first meta-analysis to assess the association between *TBXA2R* polymorphisms and asthma risk. In this meta-analysis, 7 case-control studies including 2775 cases and 1669 controls for *TBXA2R* +924C/T and 6 case-control studies including 2568 cases and 991

controls for *TBXA2R* +795C/T were analyzed. In the overall population, we found a significant association between +924C/T polymorphism and asthma risk under the recessive model. However, analysis stratified by ethnicity showed no significant association with asthma in Asians. This discrepancy may be due to different genetic backgrounds, environments and lifestyles. It needs to be further examined in larger population of different ethnicity in the future. Analysis stratified by atopic status presented a significant association between +924C/T and atopic asthma risk in the recessive model. These results suggested that +924C/T polymorphism may be a susceptibility marker for asthma, especially among atopic asthma. As for +795C/T polymorphism, no significant association was identified under any genetic models. Similar results were found in the subgroup analysis by age group. However, when we performed subgroup analysis by subphenotype, a significant increased risk of AIA was observed under the allelic model and dominant model, suggesting that +795C/T polymorphism may be related to AIA risk.

Table 2. Summary of pooled ORs in the meta-analysis.

+924C/T	N	OR (95% CI) C/T	P_H	P_Z	OR (95% CI) CC+TC/TT	P_H	P_Z	OR (95% CI) CC/TC+TT	P_H	P_Z
Overall	7	0.98(0.87–1.10)	0.081 ^a	0.854	0.89(0.77–1.03)	0.174	0.113	1.33(1.01–1.75)	0.560	0.045
Asian	6	0.92(0.81–1.05)	0.317	0.218	0.87(0.75–1.01)	0.154	0.077	1.14(0.80–1.63)	0.696	0.457
Children	4	1.02(0.76–1.39)	0.020 ^a	0.874	0.91(0.74–1.12)	0.115	0.358	1.40(0.99–1.98)	0.487	0.054
Atopic	4	1.09(0.92–1.29)	0.279	0.317	1.00(0.80–1.24)	0.689	0.975	1.43(1.01–2.01)	0.668	0.043
+795C/T		C/T			CC+TC/TT			CC/TC+TT		
Overall	6	0.97(0.87–1.09)	0.324	0.645	0.97(0.83–1.14)	0.172	0.747	0.95(0.76–1.19)	0.531	0.645
Adults	3	0.90(0.75–1.08)	0.504	0.260	0.90(0.69–1.17)	0.107	0.421	0.82(0.57–1.17)	0.620	0.272
Children	2	1.11(0.93–1.31)	0.466	0.244	1.14(0.90–1.44)	0.775	0.286	1.16(0.81–1.65)	0.281	0.416
Atopic	2	0.99(0.71–1.38)	0.075 ^a	0.958	0.93(0.59–1.46)	0.087 ^a	0.764	1.11(0.77–1.61)	0.259	0.563
AIA	3	1.30(1.05–1.60)	0.661	0.014	1.50(1.11–2.03)	0.210	0.008	1.27(0.83–1.94)	0.300	0.263

N, number of studies; OR, odds ratio; CI, confidence interval; P_H , p values of Q-test for heterogeneity; P_Z , p values of Z-test for odds ratio;

^aRandom effects model was used when p values for heterogeneity test < 0.1 , otherwise, fixed effects model was used; AIA, aspirin-intolerant asthma.

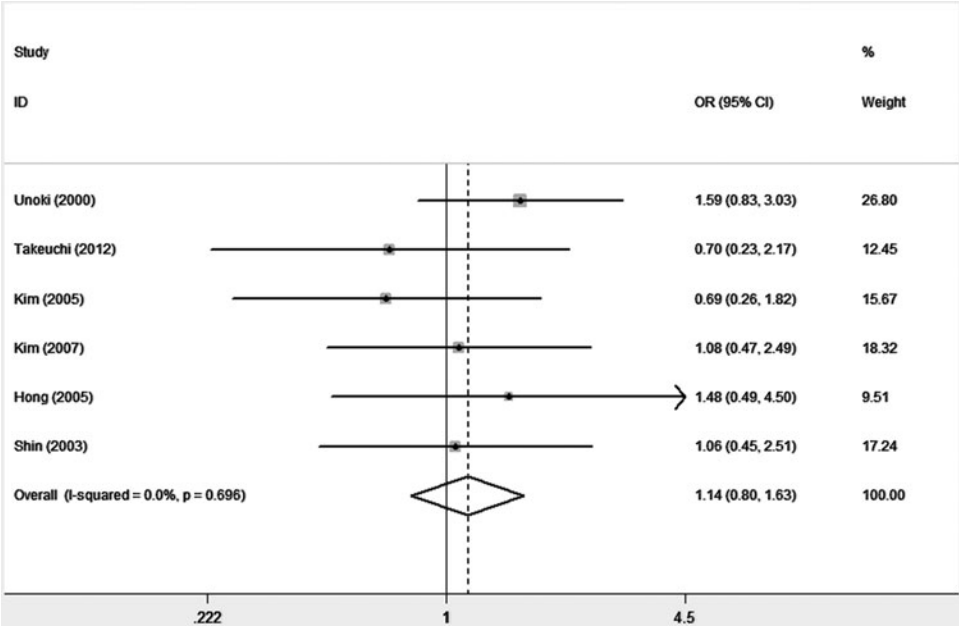


Figure 3. Forest plot of recessive comparison of *TBXA2R* +924C/T (CC vs TC + TT) in Asians in fixed effect model.

TBXA2R has been demonstrated to play an important role in the pathogenesis of inflammation and asthma. It is the main prostanoid receptor to induce bronchoconstriction in human small airways [29], in response to allergen-induced mast cell activation in atopic asthma patients [30,31]. In addition, *TBXA2R* could enhance the contraction of human bronchus induced by histamine [32]. The proliferation of ASMCs is the most significant feature of airway remodeling and closely related to the development of chronic asthma. Citro et al. [33] showed that the activation of *TBXA2R* could induce proliferation of ASMCs through the pathways of Src/Ras/ERK and Raf/MEK/ERK. Kim et al. [24] reported that a combined effect of +924C/T and +795C/T risk alleles was correlated with increased immunoglobulin E level, eosinophilic counts, and severity of asthma. Furthermore, several studies found that +924C/T polymorphism was associated with reduced lung

function indices such as forced expiratory volume in 1 second and forced expiratory flow between 25–75% in children with atopic asthma [18,23]. The major mechanism underlying bronchospasm response to aspirin in AIA patients has been explained by leukotriene excess production [34,35]. Studies have shown that ongoing TXA2 production could inhibit leukotriene synthase activity in smooth muscle cells, while aspirin could increase cysteinyl leukotrienes production in AIA patients via inhibition of formation of TXA2 [36,37]. The quantitative and structural change of *TBXA2R* may affect TXA2 and make obvious alteration in the leukotriene production in AIA patients [24]. Also, recent studies reported that *TBXA2R* was important to the amplification of pulmonary eosinophilia by leukotriene [38], and determined the sensitivity to aspirin to some extent [39]. Therefore, it is possible that *TBXA2R* +924C/T polymorphism could act as a marker for

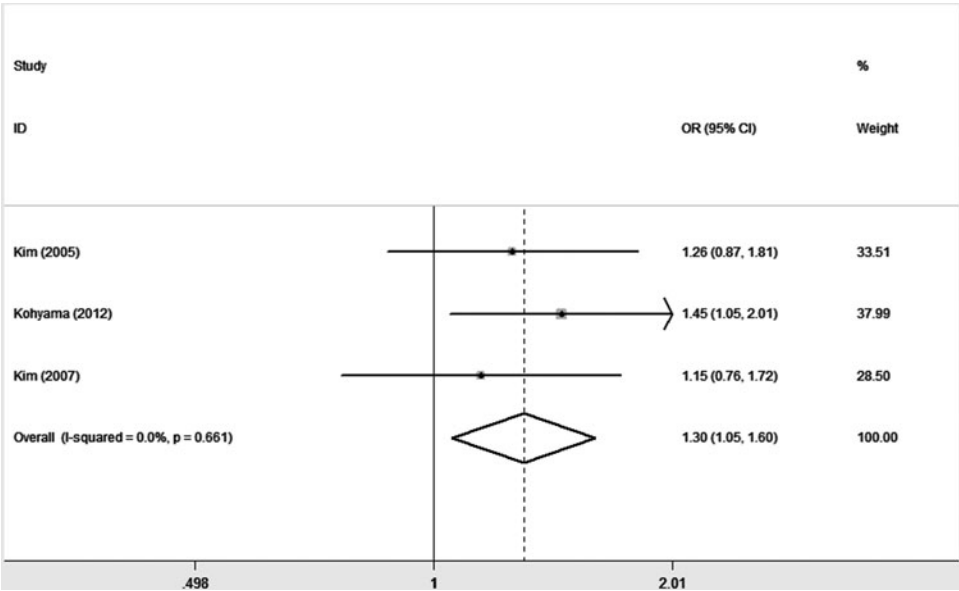


Figure 4. Forest plot of allele comparison of *TBXA2R* +795C/T (C vs T) by subgroup analysis in aspirin-intolerant asthma in fixed effect model.

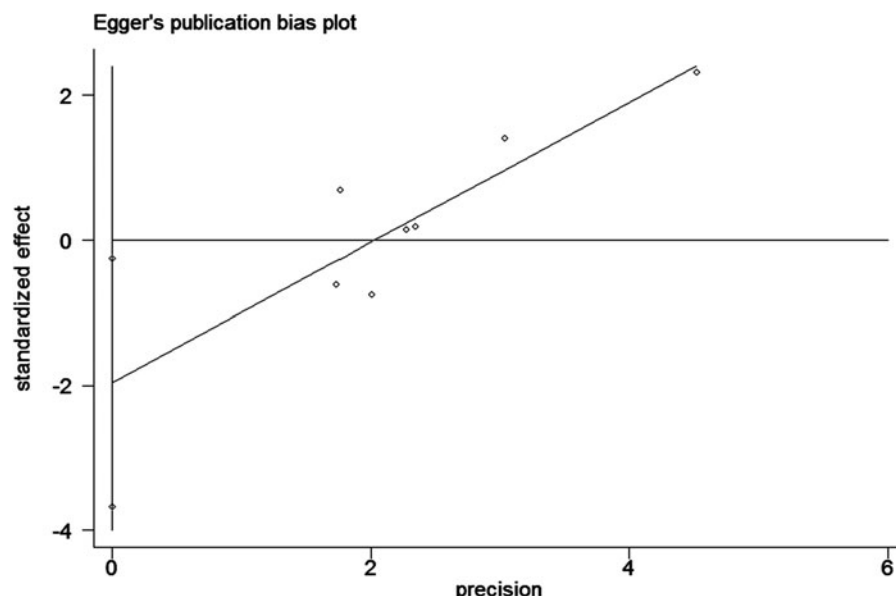


Figure 5. Egger's publication bias plot for the association between *TBXA2R* +924C/T and asthma risk under the recessive model (CC vs TC + TT).

the susceptibility to asthma and *TBXA2R* +795C/T polymorphism may be associated with increased AIA risk. The results of this meta-analysis support this hypothesis. Although both *TBXA2R* +924C/T and +795C/T polymorphisms are synonymous and may not affect *TBXA2R* protein sequence, several studies indicated that these polymorphisms might affect mRNA stability and the efficiency of receptor transcription [16–18]. Thus, future studies are needed to address mechanisms of these polymorphisms on asthma risk.

Our meta-analysis has several strengths. First, this is the first meta-analysis focused on the association between *TBXA2R* polymorphisms and the asthma susceptibility. Second, all the studies included had high qualities according to the NOS. However, some limitations should be considered. First, the number of studies included in our meta-analysis was limited. Second, asthma is a complex disease caused by multiple genetic and environmental factors, and the genetic effect would be affected by gene-gene and gene-environmental interaction. A shortage of original data limited assessment of the effects of the gene-gene and gene-environmental in the pathogenesis of asthma. Third, publication bias was observed in the comparison of *TBXA2R* +924C/T in the recessive model by Egger's linear regression analysis. Although the trim and fill analysis did not change the general result, it was impossible to completely exclude publication bias. The published studies included insufficient sample numbers and small sample sizes, and we were not able to include unpublished articles and conference papers to get data for pooled-analysis. Therefore, our study may lead to additional bias. Moreover, all included studies were published in English or Chinese indexed by the selected databases, so studies published in other languages may be missed.

In conclusion, the present meta-analysis suggested that *TBXA2R* +924C/T polymorphism is associated with asthma risk, and *TBXA2R* +795C/T polymorphism is a potential high risk factor for AIA. However, the data was limited, and the conclusion should be interpreted with caution. Well-designed studies with larger sample size adjusting for potentially confounding factors (gender, environmental factors, phenotype of

asthma etc.) are required to validate the risk identified in the current meta-analysis.

Funding

This study was supported by the National Natural Science Foundation of China (Grant No. 81070045) and the Key Clinical Project for Affiliated Hospital of Ministry of Public Health of China (Grant No. 111).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

1. Masoli M, Fabian D, Holt S, Beasley R, Program G. The global burden of asthma: executive summary of the GINA Dissemination Committee Report. *Allergy* 2004;59:469–478.
2. Kauffmann F, Demenais F. Gene-environment interactions in asthma and allergic diseases: Challenges and perspectives. *J Allergy Clin Immunol* 2012;130:1229–1240.
3. Vercelli D. Advances in asthma and allergy genetics in 2007. *J Allergy Clin Immunol* 2008;122:267–271.
4. Meyers DA. Genetics of asthma and allergy: what have we learned? *J Allergy Clin Immunol* 2010;126:439–446. quiz 47–48.
5. Finkelman FD, Vercelli D. Advances in asthma, allergy mechanisms, and genetics in 2006. *J Allergy Clin Immunol* 2007;120:544–550.
6. Miggin SM, Kinsella BT. Expression and tissue distribution of the mRNAs encoding the human thromboxane A2 receptor (TP) alpha and beta isoforms. *Biochim Biophys Acta* 1998;1425:543–559.
7. Devillier P, Bessard G. Thromboxane A2 and related prostaglandins in airways. *Fundam Clin Pharmacol* 1997;11:2–18.
8. Liu T, Laidlaw TM, Feng C, Xing W, Shen S, Milne GL, et al. Prostaglandin E2 deficiency uncovers a dominant role for thromboxane A2 in house dust mite-induced allergic pulmonary inflammation. *Proc Natl Acad Sci USA* 2012;109:12692–12697.
9. Rolin S, Masereel B, Dogne JM. Prostanoids as pharmacological targets in COPD and asthma. *Eur J Pharmacol* 2006;533:89–100.
10. Suzuki Y, Asano K, Shiraishi Y, Oguma T, Shiomi T, Fukunaga K, et al. Human bronchial smooth muscle cell proliferation via

- thromboxane A2 receptor. Prostaglandin Leukotr Essen Fat Acids 2004;71:375–382.
11. Capra V, Habib A, Accomazzo MR, Ravasi S, Citro S, Levy-Toledano S, et al. Thromboxane prostanoid receptor in human airway smooth muscle cells: a relevant role in proliferation. *Eur J Pharmacol* 2003;474:149–159.
 12. Ishimura M, Suda M, Morizumi K, Kataoka S, Maeda T, Kurokawa S, et al. Effects of KP-496, a novel dual antagonist at the cysteinyl leukotriene receptor 1 and the thromboxane A(2) receptor, on airway obstruction in guinea pigs. *Br J Pharmacol* 2008;153:669–675.
 13. Saffholm J, Dahlen SE, Adner M. Antagonising EP1 and EP2 receptors reveal that the TP receptor mediates a component of antigen-induced contraction of the guinea pig trachea. *Eur J Pharmacol* 2013;718:277–282.
 14. Hernandez JM, Janssen LJ. Revisiting the usefulness of thromboxane-A2 modulation in the treatment of bronchoconstriction in asthma. *Can J Physiol Pharmacol* 2015;93:111–117.
 15. Nakahata N. Thromboxane A2: physiology/pathophysiology, cellular signal transduction and pharmacology. *Pharmacol Ther* 2008;118:18–35.
 16. BN E. TBXA2R rSNPs, Transcriptional factor binding sites and asthma in Asians. *Open J Pediatr* 2014;4:148–161.
 17. Buroker NE. Regulatory SNPs and transcriptional factor binding sites in ADRBK1, AKT3, ATF3, DIO2, TBXA2R and VEGFA. *Transcription* 2014;5:e964559.
 18. Leung TF, Tang NL, Lam CW, Li AM, Chan IH, Ha G. Thromboxane A2 receptor gene polymorphism is associated with the serum concentration of cat-specific immunoglobulin E as well as the development and severity of asthma in Chinese children. *Pediatr Allergy Immunol* 2002;13:10–17.
 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;25:603–605.
 20. Unoki M, Furuta S, Onouchi Y, Watanabe O, Doi S, Fujiwara H, et al. Association studies of 33 single nucleotide polymorphisms (SNPs) in 29 candidate genes for bronchial asthma: positive association a T924C polymorphism in the thromboxane A2 receptor gene. *Hum Genet* 2000;106:440–446.
 21. Kim SH, Choi JH, Park HS, Holloway JW, Lee SK, Park CS, et al. Association of thromboxane A2 receptor gene polymorphism with the phenotype of acetyl salicylic acid-intolerant asthma. *Clin Exp Allergy* 2005;35:585–590.
 22. Shin HD, Park BL, Jung JH, Wang HJ, Park HS, Choi BW, et al. Association of thromboxane A2 receptor (TBXA2R) with atopy and asthma. *J Allergy Clin Immunol* 2003;112:454–457.
 23. Hong SJ, Lee SY, Kim HB, Kim JH, Kim BS, Choi SO, et al. IL-5 and thromboxane A2 receptor gene polymorphisms are associated with decreased pulmonary function in Korean children with atopic asthma. *J Allergy Clin Immunol* 2005;115:758–763.
 24. Kim JH, Lee SY, Kim HB, Jin HS, Yu JH, Kim BJ, et al. TBXA2R gene polymorphism and responsiveness to leukotriene receptor antagonist in children with asthma. *Clin Exp Allergy* 2008;38:51–59.
 25. Takeuchi K, Mashimo Y, Shimojo N, Arima T, Inoue Y, Morita Y, et al. Functional variants in the thromboxane A2 receptor gene are associated with lung function in childhood-onset asthma. *Clin Exp Allergy* 2013;43:413–424.
 26. Murk W, Walsh K, Hsu LI, Zhao LL, Bracken MB, DeWan AT. Attempted replication of 50 reported asthma risk genes identifies a SNP in RAD50 as associated with childhood atopic asthma. *Hum Hered* 2011;71:97–105.
 27. Kim SH, Kim YK, Park HW, Jee YK, Kim SH, Bahn JW, et al. Association between polymorphisms in prostanoid receptor genes and aspirin-intolerant asthma. *Pharmacogenet Genom* 2007;17:295–304.
 28. Kohyama K, Hashimoto M, Abe S, Kodaira K, Yukawa T, Hozawa S, et al. Thromboxane A2 receptor +795T>C and chemoattractant receptor-homologous molecule expressed on Th2 cells –466T>C gene polymorphisms in patients with aspirin-exacerbated respiratory disease. *Mol Med Rep* 2012;5:477–482.
 29. Saffholm J, Manson ML, Bood J, Delin I, Orre AC, Bergman P, et al. Prostaglandin E inhibits mast cell-dependent bronchoconstriction in human small airways through the E prostanoid subtype 2 receptor. *J Allergy Clin Immunol* 2015;136:1232–1239.
 30. Daham K, James A, Balgoma D, Kupczyk M, Billing B, Lindeberg A, et al. Effects of selective COX-2 inhibition on allergen-induced bronchoconstriction and airway inflammation in asthma. *J Allergy Clin Immunol* 2014;134:306–313.
 31. Sladek K, Dworski R, Fitzgerald GA, Buitkus KL, Block FJ, Marney SR. Jr., et al. Allergen-stimulated release of thromboxane A2 and leukotriene E4 in humans. Effect of indomethacin. *Am Rev Resp Dis* 1990;141:1441–1445.
 32. Knight DA, Stewart GA, Thompson PJ. Histamine-induced contraction of human isolated bronchus is enhanced by endogenous prostaglandin F2 alpha and activation of TP receptors. *Eur J Pharmacol* 1997;319:261–267.
 33. Citro S, Ravasi S, Rovati GE, Capra V. Thromboxane prostanoid receptor signals through G(i) protein to rapidly activate extracellular signal-regulated kinase in human airways. *Am J Resp Cell Mol* 2005;32:326–333.
 34. Antczak A, Montuschi P, Kharitonov S, Gorski P, Barnes PJ. Increased exhaled cysteinyl-leukotrienes and 8-isoprostane in aspirin-induced asthma. *Am J Respir Crit Care Med* 2002;166:301–306.
 35. Celik G, Bavbek S, Misirligil Z, Melli M. Release of cysteinyl leukotrienes with aspirin stimulation and the effect of prostaglandin E(2) on this release from peripheral blood leucocytes in aspirin-induced asthmatic patients. *Clin Exp Allergy* 2001;31:1615–1622.
 36. Tornhamre S, Ehnage A, Kolbeck KG, Edenius C, Lindgren JA. Uncoupled regulation of leukotriene C4 synthase in platelets from aspirin-intolerant asthmatics and healthy volunteers after aspirin treatment. *Clin Exp Allergy* 2002;32:1566–1573.
 37. Lupinetti MD, Sheller JR, Catella F, Fitzgerald GA. Thromboxane biosynthesis in allergen-induced bronchospasm. Evidence for platelet activation. *Am Rev Resp Dis* 1989;140:932–935.
 38. Liu T, Garofalo D, Feng C, Lai J, Katz H, Laidlaw TM, et al. Platelet-driven leukotriene C4-mediated airway inflammation in mice is aspirin-sensitive and depends on T prostanoid receptors. *J Immunol* 2015;194:5061–5068.
 39. Fontana P, Zufferey A, Daali Y, Reny JL. Antiplatelet therapy: targeting the TxA2 pathway. *J Cardiovasc Translat Res* 2014;7:29–38.