

Association of the IL-4R Q576R Polymorphism with Pediatric Asthma: a meta-analysis

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Abstract

Background: The relationship between Q576R polymorphism of IL-4 receptor (IL-4R) gene and pediatric asthma risk is still undefined. To this end, this meta-analysis was performed to explore the above controversy.

Methods: In this study, we systemically retrieved CNKI, EMBASE, Web of Science, Scopus, Science direct and Pub Med to collect relevant researches, followed by calculation of odds ratio (OR) along with 95% confidence intervals (CIs). STATA 12.0 software was employed in this meta-analysis.

Results: We found an association between IL-4R Q576R polymorphism and pediatric asthma risk (GG vs AA: OR = 3.75, 95% CI = 1.89-7.45; AG vs AA: OR = 2.15, 95% CI = 1.36-3.39; the dominant model: OR = 2.25, 95% CI = 1.42-3.57; the recessive model: OR = 3.05, 95% CI = 1.54-6.05). Moreover, there was no obvious publication bias.

Conclusion: Our findings suggested that G allele of IL-4R Q576R polymorphism is associated with increased risk of pediatric asthma. Anyhow, delicately-designed, large-scale studies should be conducted to further confirm the current outcomes.

Keywords: IL-4, Asthma, Meta-analysis.

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Introduction

Asthma is a common chronic allergic disorder that involves the respiratory tract and affects millions of children worldwide. With the detection rate up to 10% of children, atopic asthma is a global public health problem¹. The complex pathogenesis of asthma is still unclarified. However, decreased lung function, allergic disorder, bacterial and viral infections are currently considered as the main causes for the persistence as well as progression of asthma²⁻⁶. Additionally, according to epidemiological researches, there is certain association between asthma etiology and genetic risk factors⁷. Genetic risk factors for adult-onset asthma are largely a subset of the genetic risk for childhood-onset asthma but with overall smaller effects, suggesting a greater role for non-genetic risk factors in adult-onset asthma⁸. Moreover, parental asthma is

a potent predictive factor for pediatric asthma, suggesting the potent genetic basis of pediatric asthma⁹.

Interleukin 4 (IL-4) not only is vitally involved in type 2 T-helper (Th2) reactions and isotype class switching of B cells to IgE synthesis, but participates in the recruitment of mast cells¹⁰. IL-4 receptor (IL-4R) is a transmembrane protein containing two subunits, namely α and γ chains. Moreover, accumulative studies have supported the critical functions of IL-4R in asthma pathogenesis and IgE level regulation. The binding between IL-4 protein and IL-4R triggers tyrosine system activation, which subsequently activates signal transducer and activator of transcription 6 (STAT6), thereby elevating the level of IL-4-sensitive genes, including IgE, MHC-II as well as CD23¹¹.

IL-4R gene has been previously demonstrated as a potential asthma-related gene, located on chromosome 16p12.1. IL-4R Q576R polymorphism (rs1801275) was first revealed by Hershey et al. in 1997, which was potentially correlated with atopy¹². IL-4R Q576R polymorphism of exon region gives rise to the glutamine-to-arginine substitution IL-4R α protein, which is present on the cytoplasmic domain. At present, IL-4R Q576R polymorphism has been demonstrated to be associated with a se-

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ries of disorders, such as bronchiolitis, periodontitis and atopic dermatitis¹³⁻¹⁵.

Further investigations have indicated the possible relationship of IL-4R Q576R polymorphism with pediatric asthma, however, the conclusion is drawn from studies with inadequate statistical power, sample size and clinical heterogeneity. To this end, the present meta-analysis was performed to accurately examine the correlation of IL-4R Q576R polymorphism with pediatric asthma risk.

Methods

Identification of studies

Two investigators (Xiwu Chen and Jinhui Hu) screened each of the titles, abstracts and full texts to determine inclusion independently. The results were compared and disagreements were resolved by consensus. We systematically searched in Embase, Pub Med, Web of Science, Scopus, Science direct and CNKI databases with several key words: 'interleukin 4/IL-4', '576R', 'pediatric asthma', and 'gene polymorphism' (last search was updated on October 2021). Additional manual screening of references from reviewed studies was supplemented to comprehensively extract all relevant researches. Moreover, an information flowchart was constructed, covering screening, identification, eligibility and final selections based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines¹⁶. The protocol is registered in PROSPERO (ID: 283601).

Inclusion criteria and data extraction

Eligible researches were collected accordingly: i) All studies concerning the association between IL-4R Q576R polymorphism and pediatric asthma risk; ii) researches with adequate and effective genotype information; iii) We defined childhood asthma using strict age of onset criteria and considered asthma cases with onset < 12 years of age as childhood onset cases⁸. Additionally, comparisons of animal study, laboratory approaches, interim analysis and researches with overlapping populations were eliminated.

Data extraction

Necessary data were retrieved from all eligible researches by two independent investigators with agreement on all items (Xiwu Chen and Jinhui Hu), including: first author name, year of publication, region, number and genotypes of cases and controls, ethnicity and evidence of Hardy-Weinberg equilibrium (HWE) in controls.

Quality assessment

Newcastle-Ottawa Scale (NOS) was employed to evaluate the methodological quality of every enrolled research¹⁷, where a final score of or over six stars was taken for high-quality.

Statistical analysis

The deviation from HWE for the distribution of every genotype in control group was determined by Fisher exact test. In addition, odds ratio (OR) along with 95% confidence interval (95%CI) was adopted to assess the degree of correlation between IL-4R Q576R polymorphism and vulnerability to pediatric asthma under Dominant (GG+GA vs. AA), Additive (GG vs. AA, GA vs. AA) and Recessive (GG vs. AA+GA) models between groups. I² test was subsequently employed to evaluate the heterogeneity among researches, where I² > 50% implicated heterogeneity as well as application of random effects model, otherwise fixed effects model should be performed. Sensitivity analysis was mainly conducted by sequentially omitting each study or non-HWE ones. Finally, the possible publication bias was visually assessed by Begg's funnel plot. STATA 12.0 (Stata Corp LP, College Station, TX, USA) was employed for statistical analysis and a P value < 0.05 indicated statistical significance. The power of each study was computed as the probability of detecting an association between IL-4R Q576R polymorphism and pediatric asthma using a significance level of 0.05, assuming an OR of 1.5 (small effect size). Power analysis was performed using the statistical program PS: Power and Sample Size Calculation (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>).

Trial sequential analysis

Meta-analysis might be affected by the increased risk of random errors and repeated significance testing. TSA can increase the robustness of the conclusions by estimating the amount of the required information size (RIS) and the threshold for statistical significance. During the analysis, the significance levels for type I and type II errors were set to 5% and 20%, respectively, and relative risk reduction (RRR) was set at 20%. When the cumulative Z-curve crosses the TSA boundary or enters the insignificance area, it demonstrates a sufficient level of evidence, and no further study is necessary. The TSA software (version 0.9.5.10 beta) was used for data processing¹⁸.

Results

Study characteristics

The flow diagram concerning study selection was displayed in Figure 1. 181 studies were initially identified, and 169 of them were eliminated after reviewing title or abstract. Moreover, one, two and another two studies were eliminated due to no full-text, not case-control studies and inaccessible necessary information, respectively. Eventually, seven researches were enrolled in our

meta-analysis, including a total of 912 cases and 708 controls¹⁹⁻²⁵. Except for the study by Zheng et al., the genotype distribution was consistent with HWE in control populations. All included studies used PCR-RFLP method. The main features of these researches were displayed in Table 1. NOS score of all studies were higher than six stars was taken for high-quality studies. The statistical powers of these 7 studies ranged from 18.2% to 49%. None of the studies had a statistical power that exceeded 80%.

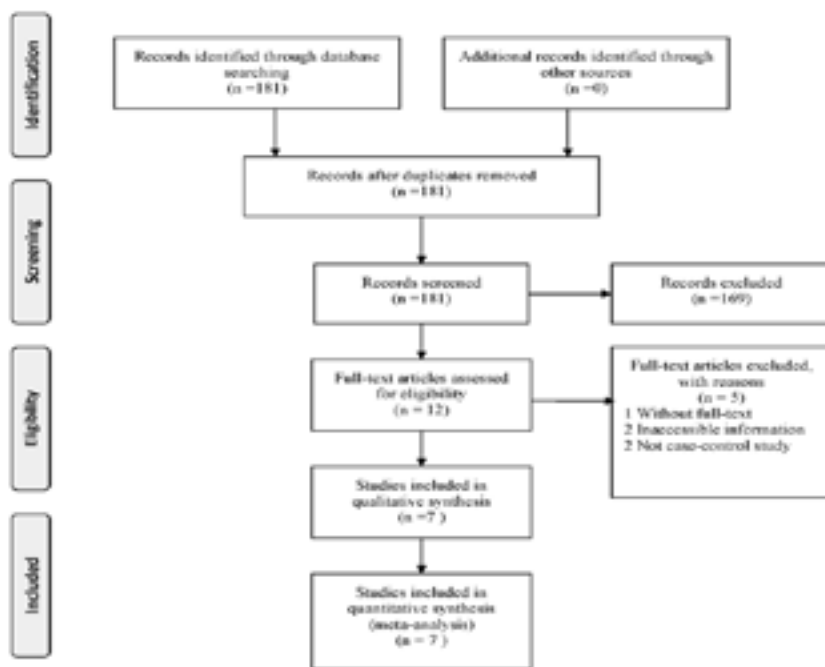


Figure 1. The flow diagram of included/excluded studies.

Table 1: Characteristics of the included studies for meta-analysis

Study included	Year	Area	Race	Cases/ Controls	Genotypes for cases			Genotypes for controls			HWE test
					AA	AG	GG	AA	AG	GG	
Cui et al	2005	China	Asians	143/72	77	52	14	55	16	1	0.89
Liu et al	2005	China	Asians	76/60	46	27	3	47	12	1	0.82
Zhang et al	2006	China	Asians	94/68	55	39	0	57	11	0	0.46
Dai et al	2010	China	Asians	96/96	47	48	1	62	33	1	0.13
Sun et al	2010	China	Asians	91/42	67	24	0	33	9	0	0.44
Wu et al	2010	China	Asians	252/227	183	61	8	168	55	4	0.84
Zheng et al	2014	China	Asians	160/143	94	51	15	125	14	4	0.00

HWE, Hardy–Weinberg equilibrium

Meta-analysis results

The major outcomes of our meta-analysis were shown in Figure 2. Q576R polymorphism was significantly correlated with elevated risk of pediatric asthma (GG vs. AA: OR = 3.75, 95% CI = 1.89-7.45; AG vs. AA: OR

= 2.15, 95% CI = 1.36-3.39; the dominant model: OR = 2.25, 95% CI = 1.42-3.57; the recessive model: OR = 3.05, 95% CI = 1.54-6.05). The final result remained unchanged after eliminating the non-HWE research stratification analysis, suggesting the reliability and stability of our findings.

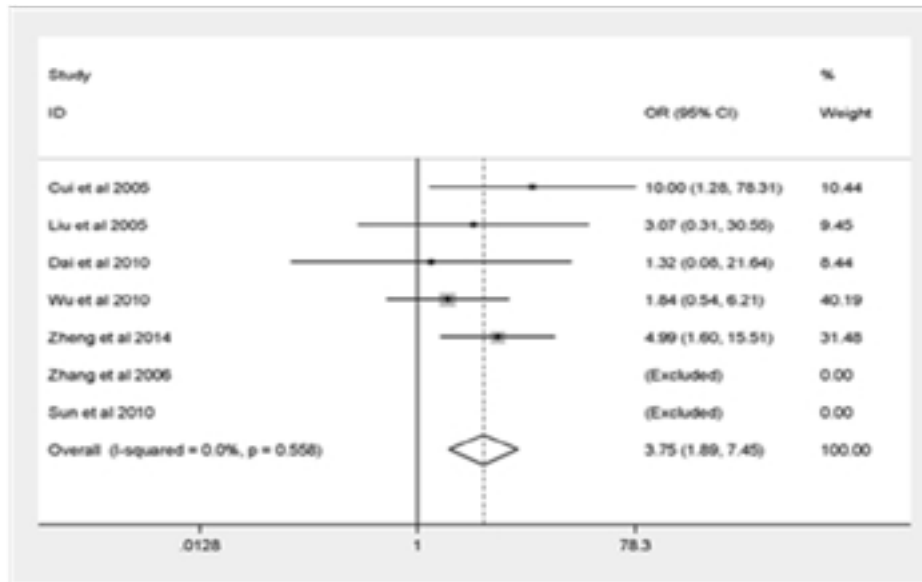


Figure 2. Forest plot for meta-analysis of the association between the IL-4R Q576R polymorphism and pediatric asthma risk(GG vs AA).

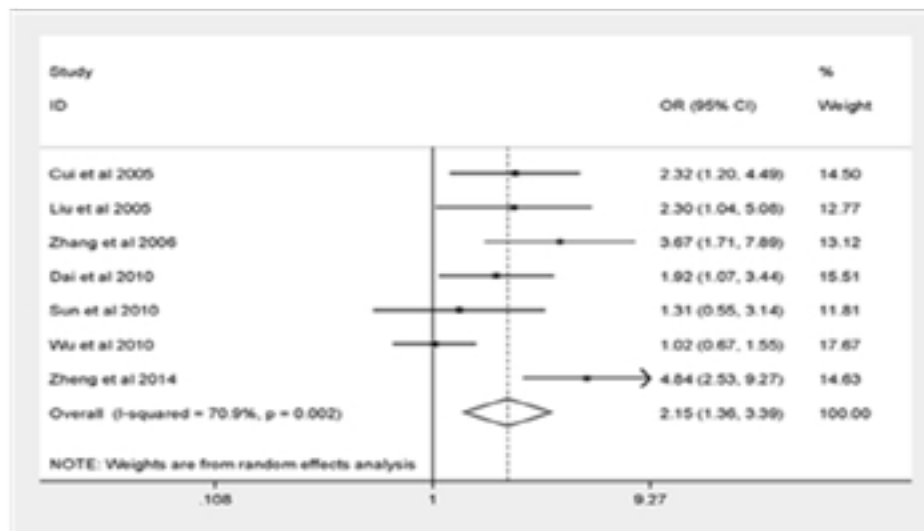


Figure 2. Forest plot for meta-analysis of the association between the IL-4R Q576R polymorphism and pediatric asthma risk(AG vs AA).

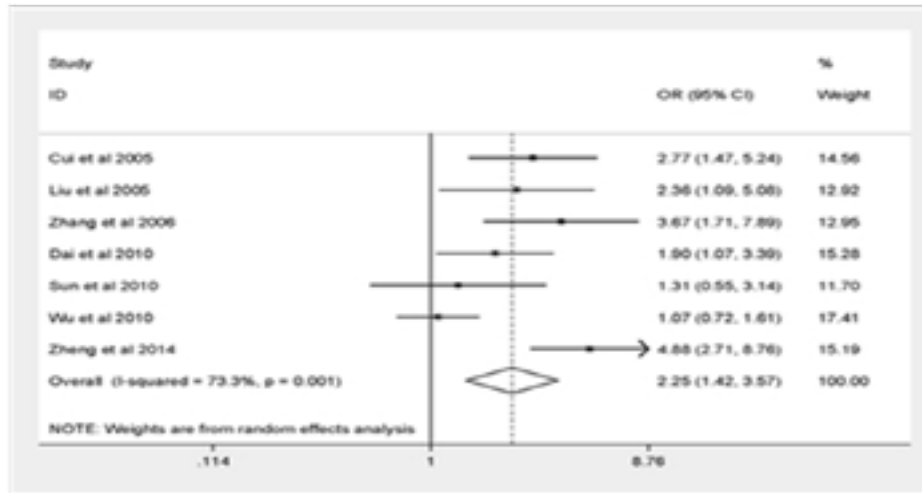


Figure 2. Forest plot for meta-analysis of the association between the IL-4R Q576R polymorphism and pediatric asthma risk(Dominant model).

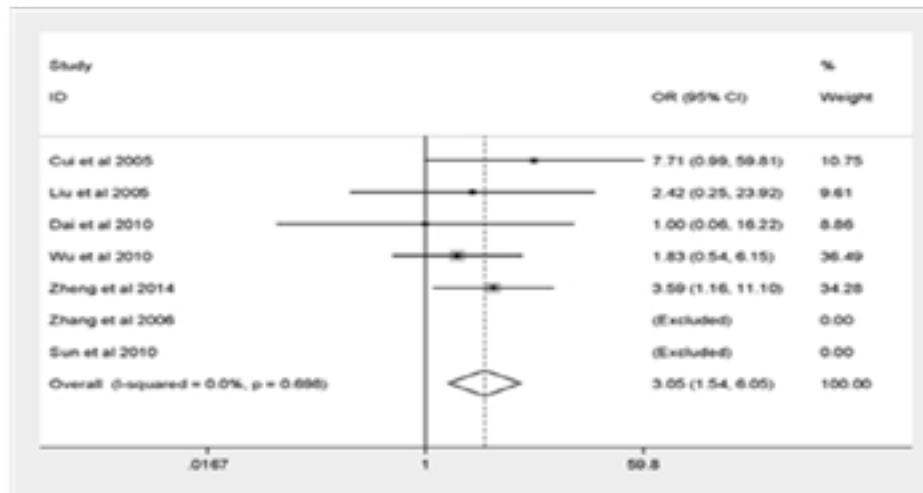


Figure 2. Forest plot for meta-analysis of the association between the IL-4R Q576R polymorphism and pediatric asthma risk(Recessive model).

Publication bias

The Begg's test was performed for evaluating publication

bias. Consequently, there no obvious evidence of publication bias by visually assessing funnel plot (Figure 3), implicating the low publication bias of our meta-analysis.

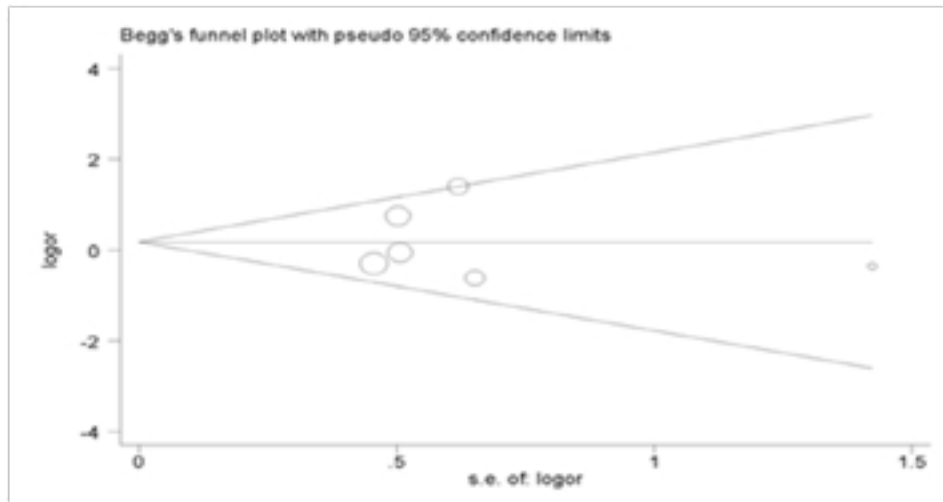


Figure 3. Begg's funnel plot analysis to detect potential publication bias for IL-4R Q576R polymorphism(GG vs AA).

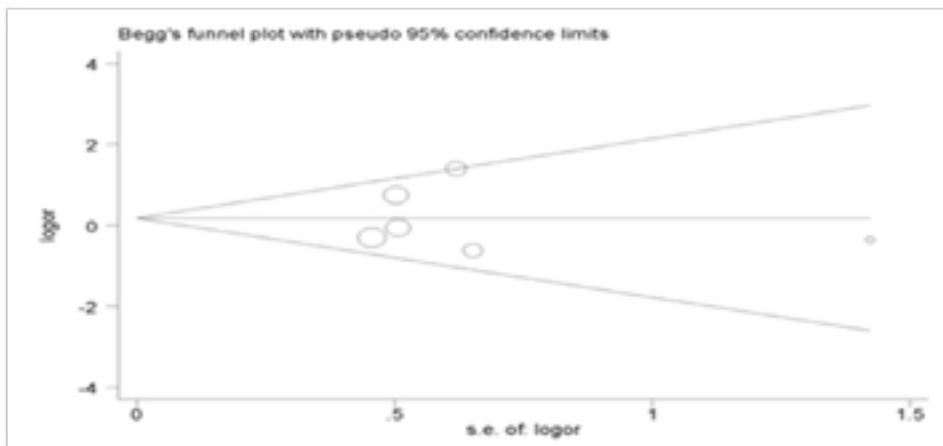


Figure 3. Begg's funnel plot analysis to detect potential publication bias for IL-4R Q576R polymorphism(AG vs AA).

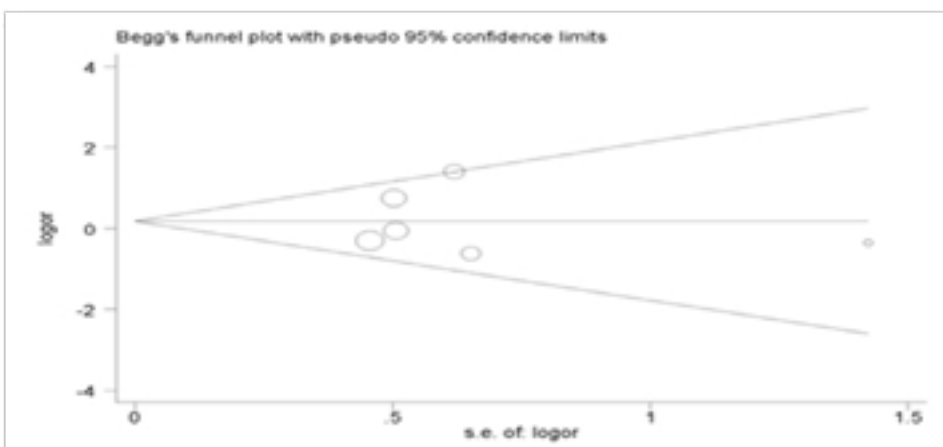


Figure 3. Begg's funnel plot analysis to detect potential publication bias for IL-4R Q576R polymorphism(Dominant model).

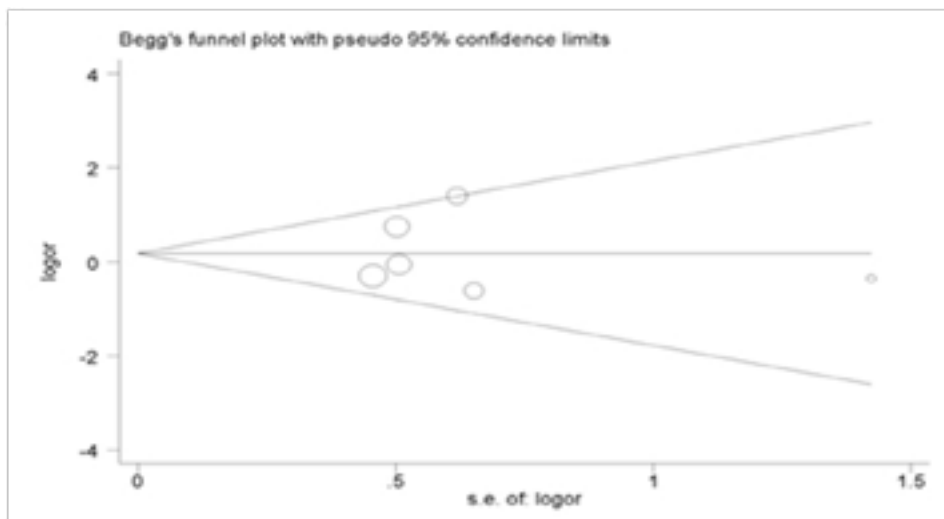


Figure 3. Begg's funnel plot analysis to detect potential publication bias for IL-4R Q576R polymorphism (Recessive model).

Trial Sequential Analysis

For reducing the random errors and increasing the credibility of the conclusions, TSA was performed. It showed that the cumulative Z-curves did not cross monitoring

boundaries and futility boundaries and also did not reach the required information size (Figure 4). Thus, the results were potential false negative in additive models (GG vs. AA), and more studies were needed to conduct.

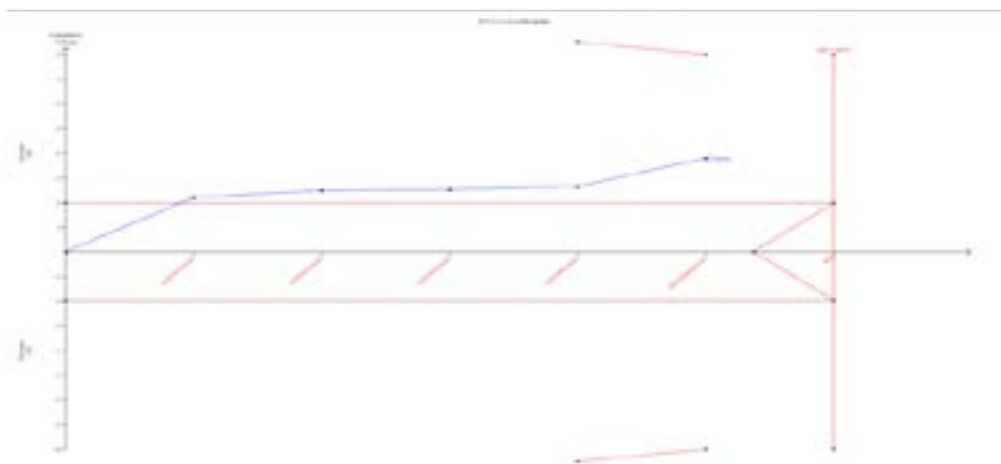


Figure 4. TSA for IL-4R Q576R polymorphism. We calculated a-spending adjusted required information size (RIS) by using $\alpha = 0.05$ (two-sided), power = 80%. The cumulative Z-curve (Blue); Conventional boundary (Deep red); TSA boundary (red).

Discussion

Asthma is considered as the most prevalent chronic pediatric disorder. The complicated pathogenesis of asthma remains largely unclear, despite multiple genetic loci as well as diverse environmental factors which are indicated to play decisive roles²⁶. Genetic association study is considered as an effective way to determine asthma susceptibility associated with SNPs of candidate genes and has been widely applied in asthma research. However, the studies including inadequate samples may have weak statistical power and thereby interfere with the precision of results, leading to false positive or false negative findings consequently. Here, we performed a meta-analysis of published studies to evaluate the association between IL-4R Q576R polymorphism and risk of pediatric asthma. In conclusion, we found that IL-4R Q576R polymorphism might contribute to pediatric asthma risk.

Previous meta-analysis showed that IL-4R Q576R polymorphism is associated with asthma, included adults and children, but there was no subgroup analysis aiming at age in this article²⁷. In the largest asthma GWAS to date, genetic risk loci for adult onset asthma is largely a subset of the loci associated with childhood onset asthma, with overall smaller effect sizes for onset at later ages⁸. Because childhood asthma is highly related to genes compared with adult asthma, we perform this meta-analysis for pediatric asthma. In conclusion, our findings showed that G allele of IL-4R Q576R polymorphism is associated with increased risk of pediatric asthma. In consideration of the possible between-study heterogeneity caused by deviation of allelic distributions from HWE, sensitivity analyses (only those consistent with HWE were analyzed by meta-analysis) were conducted, showing that the meta-analysis was reliable and realistic. Additionally, no evidence owed possible publication bias in our study. Nevertheless, the mechanism underlying the relationship between IL-4R Q576R polymorphism and pediatric asthma risk remains unknown. To be specific, IL-4R-encoded protein is a vital functional component of Th2 cells. Previous study showed that The IL-4R Q576R polymorphism may involve in the development of allergy through modulating specific serum IgE levels²⁸. While IL-4R-deficient mice cannot generate IgE and show defective Th2 responses, implicating that IL-4R plays a critical role in regulating IgE, and Q576R polymorphism could influence signal transduction, thereby elevating asthma risk.²⁸

In addition, the possible effect of Q576R polymorphism could be influenced by gene-gene interaction. Previous study showed that IL-4-C33T, IL-13 R130Q, IL-4R I75V, IL-4R Q576R, STAT6 C2892T, and CD14-C159T may synergistically enhance the vulnerability to pediatric asthma²⁹. Interaction between other risk factors and this polymorphism in relation to pediatric asthma should be further studied.

There were several limitations in our study. To begin with, based on unadjusted information, we were unable to obtain genotype data after stratification for major confounding factors; additionally, there was great variation on confounding factors among different researches. Secondly, only seven articles from China were selected in the present meta-analysis. This may be one of the main limitations of the present work. Thirdly, with the merely published studies included in our meta-analysis, publication bias is very likely to occur, though no statistically significant publication bias is found in our meta-analysis. Fourth, age could be an important one, as the results for outcome onset before school age, before adolescence, and puberty can be different. Due to the small number of articles, we could not conduct a subgroup analysis for age. Finally, the predictive value of a single gene test in a complex disease is very limited for diagnostic or preventive purposes and thus cannot be recommended. Based on data of simulation studies and other complex diseases, the use of genetic profiling that incorporates multiple genetic risk factors holds promise for clinical application.

The results of genome-wide association studies will be crucial in establishing this genetic risk profile for asthma. In the future, asthma prediction may be possible, based on a prediction model that incorporates genes, personal factors and environmental risk factors³⁰. In conclusion, we demonstrate the significant relationship of IL-4R Q576R polymorphism with pediatric asthma. Population-based, large-scale, case-control studies should be performed to confirm the identified risk factors in our study, and to further explore other potential gene-environment and gene-gene interactions on pediatric asthma risk.

Compliance with Ethical Standards

Research involving human participants and/or animals not applicable.

Declaration of conflicting interests

None.

References

1. Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol*. 2015;16: 45-56.
2. Alizadeh Z, Mortaz E, Adcock I, Mostafa Moin. Role of epigenetics in the pathogenesis of asthma. *Iran J Allergy Asthma Immunol*. 2017; 16: 82-91.
3. Erika von Mutius. Gene-environment interactions in asthma. *J Allergy Clin Immunol*. 2009; 123: 3-11.
4. Toskala E, Kennedy DW. Asthma risk factors. *Int Forum Allergy Rhinol*. 2015;5: S11-16.
5. Qihong Deng, Chan Lu, Yuguo Li, Jan Sundell, Dan Norbäck. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. *Environmental Research*. 2016;150:119-27.
6. Deng Q, Lu C, Norbäck D. Early life exposure to ambient air pollution and childhood asthma in China. *Environ Res*. 2015;143:83-92.
7. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007;81:559-75.
8. Milton Pividori, Nathan Schoettler, Dan L Nicolae, et al. Shared and distinct genetic risk factors for childhood-onset and adult-onset asthma: genome-wide and transcriptome-wide studies. *Lancet Respir Med* 2019;7:509-22.
9. Litonjua AA, Carey VJ, Burge HA, et al. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med* 1998;158:176-81.
10. Maes T, Joos G, Brusselle G. Targeting Interleukin-4 in Asthma: Lost in Translation? *Am J Respir Cell Mol Biol* 2012;47:261-70.
11. Nelms K, Keegan AD, Zamorano J, et al. (1999). The IL-4 receptor: signaling mechanisms and biologic functions. *Ann Rev Immunol* 1999;17: 701-38.
12. Hershey GK, Friedrich MF, Esswein LA, et al. The association of atopy with a gain-of-function mutation in the alpha subunit of the interleukin-4 receptor. *N Engl J Med* 1997; 337: 1720-5.
13. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol* 2000;142: 1003-6.
14. Huang ZY, Dong L, Chen BJ, et al. A case-control study on association between IL-4 receptor alpha gene polymorphisms and respiratory syncytial virus bronchiolitis. *Chin J Birth Health & Hered* 2010;18: 7-9.
15. Reichert S, Stein JM, Klapproth J, et al. The genetic impact of the Q551R interleukin-4 receptor alpha polymorphism for aggressive or chronic periodontitis and the occurrence of periodontopathic bacteria. *Arch Oral Biol* 2011;56: 1485-93.
16. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
17. 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; 25:603-5.
18. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. *BMC Med Res Methodol* 2017;17:39.
19. Cui TP, Hu LH, Pan SX, et al. Polymorphisms in IL-4 and IL-4R genes in children with allergic asthma. *Chin J Pathophysiol* 2005;21:125-8.
20. Liu LN, Zhang YW. Study on relationship between asthma and polymorphisms of Interleukin-4 receptor and Interleukin-4. *J Medical Forum* 2005; 26: 38-40.
21. Sun J, Yu XH, Chen Y, et al. Relationship between polymorphisms of interleukin-4 receptor gene and childhood asthma in Harbin. *J Clin Pediatr* 2010; 28: 138-41.
22. Zhang AM, Li HL, Hao P, et al. Association of Q576R polymorphism in the interleukin-4 receptor gene with serum IgE levels in children with asthma. *Zhongguo Dang Dai Er Ke Za Zhi* 2006;8: 109-12.
23. Dai H, Liu QH, Hua L, et al. Association between asthma and single nucleotide polymorphisms in children from Shanghai. *J Clin Pediatr* 2010;28: 1039-42.
24. Wu XH, Li Y, Chen Q, et al. Association and gene-gene interactions of eight common single-nucleotide polymorphisms with pediatric asthma in middle China. *J Asthma* 2010;47: 238-44.
25. Zheng S, Zhu X, Li B, et al. Correlation of gene polymorphism of interleukin 4 receptor alpha peptide chain and total serum IgE levels in asthmatic children in Guiyang area. *Zhonghua Yi Xue Za Zhi* 2014;94:2822-7.
26. Sengler C, Lau S, Wahn U, et al. Interactions between genes and environmental factors in asthma and atopy: new developments. *Respir Res* 2002;3:7.
27. Zhu N, Gong Y, Chen XD, et al. Association between the polymorphisms of interleukin-4, the interleukin-4 receptor gene and asthma. *Chin Med J (Engl)* 2013;126:2943-51.

28. Qiao HL, Yang J, Zhang YW. Relationships between specific serum IgE, cytokines and polymorphisms in the IL-4, IL-4R α in patients with penicillins allergy. *Allergy* 2005;60:1053-9.
29. Barner M, Mohrs M, Brombacher F, et al. Differences between IL-4R α -deficient and IL-4-deficient mice reveal a role for IL-13 in the regulation of Th2 responses. *Curr Biol* 1998;8: 669-72.
30. Koppelman GH, te Meerman GJ, Postma DS. Genetic testing for asthma. *Eur Respir J* 2008;32:775-82.