Association of the *IL-4R* Q576R polymorphism with asthma: a meta-analysis

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Abstract

Introduction: Several studies have examined the relationship of IL-4 receptor gene (*IL-4R*) polymorphisms with asthma, yet the results remain inconsistent. This may be attributed to the small sample sizes and the polymorphism's small effect size, which fail to offer potent statistical power. Therefore, this meta-analysis on related studies was aimed at analyzing how *IL-4R* Q576R polymorphisms affected the asthma susceptibility.
Material and methods: Databases including Web of Science, PubMed, Google Scholar, CNKI and EMBASE were systematically searched in order to retrieve pertinent studies. Odds ratios (ORs) and the relevant 95% confidence intervals (CIs) were also calculated.
Results: Collectively, 12 eligible articles involving 1553 patients and 1904 normal subjects were subjected to analysis. There was no distinct relationship between *IL-4R* Q576R polymorphism and asthma susceptibility, in the entire study population (R vs. Q: OR = 1.25, 95% CI: 0.98–1.59; RQ vs. QQ: OR = 1.21, 95% CI: 0.98–1.49; RR vs. QQ: OR = 1.47, 95% CI: 0.80–2.71; the recessive model: OR = 1.38, 95% CI: 0.80–2.40; the dominant model: OR = 1.25, 95% CI: 0.98–1.60). Subgroup analysis, conducted based on ethnicity and study population, revealed no obvious interrelation.
Conclusions: Our findings demonstrated no relationship between *IL-4R* Q576R polymorphism and asthma susceptibility. More well-designed and large-scale studies are needed to validate the above findings.

Key words: IL-4R, asthma, meta-analysis.

Introduction

Asthma is a chronic airway inflammatory disease, presenting with reversible bronchospasm and airflow obstruction. With the world currently witnessing 300 million asthma cases, it is predicted that the figure will hit 400 million by 2025 [1, 2]. Asthma, being a multi-factorial disorder, is induced by the interactions between diverse environmental and genetic factors, with a heritability of about 35–75% reported [3, 4]. Therefore, to explore the possible role of genetic susceptibility in asthma pathogenesis, several studies have identified over 100 genes in this regard [5].

Interleukin-4 (IL-4) is implicated in B-cell isotype class switching to generate IgE and a type 2 immune response, which in turn recruits the mast cells [6]. This is suggestive of its key role in asthma genesis and progression. IL-4 receptor (IL-4R), one of the transmembrane proteins, contains the α- and γ-chain subunits. IL-4R is increasingly suggested to have

an important function in asthma pathogenesis and IgE regulation. In response to the binding of IL-4 protein to IL-4R, the triggered tyrosine system activates STAT6, thus promoting IL-4 sensitive gene expression, such as that of *CD23*, MHC class II, or *IgE* [7].

The *IL-4R* gene has been identified as a potential asthma-related gene. As for the IL-4Rα subunit, its encoding gene can be detected on chromosome 16p12.1 (GenBank Accession No. NM000418). *IL-4R* Q576R polymorphism (rs1801275) was initially detected by Hershey and colleagues, who discovered that the *IL-4R* 576R allele was associated with atopy [8]. Such polymorphisms can be detected in *IL-4R*'s exonic region; this allelic variation may result in the replacement of glutamine by arginine within IL-4Rα's cytoplasmic domain. Notably, the *IL-4R* Q576R polymorphism is related to some disorders, such as chronic periodontitis and bronchiolitis [9].

Several studies have been carried out to examine the relationship between *IL-4R* Q576R polymorphism and asthma risk. However, their inconsistent findings may be associated with limited study samples and the polymorphism's small effect size, lacking potent statistical power to establish this relationship. Thus, the present meta-analysis was conducted to assess this association.

Material and methods

We carried out this meta-analysis, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [10]. Ethical committee approval was waived due to the absence of human or animal experiment in this study. The protocol is registered in PROSPERO (ID:327938).

Search strategy

The databases Web of Science, PubMed, Google Scholar, CNKI and EMBASE were systemically searched to identify the candidate studies concerning the relation of *IL-4R* Q576R polymorphism with asthma susceptibility from inception to July 2021. The keywords used were as follows: ("asthmatic" or "asthma" [Mesh]), ("interleukin 4," "IL-4," or "interleukin-4"), and ("polymorphisms," "SNP," "single nucleotide polymorphism," "variation," or "mutation"). In addition, relevant references were also manually searched to identify related articles.

Eligibility criteria

Studies were considered eligible if they fulfilled the following inclusion criteria: (1) assessment of *IL-4R* Q576R polymorphisms as well as asthma susceptibility, (2) case-control studies, and (3) sufficient genotype data. Studies were excluded based on the following criteria: (1) studies irrelevant to asthma, (2) reviews, (3) articles without sufficient data, and (4) duplicates.

Data collection

Two reviewers independently screened relevant studies and extracted the required data. Disagreements between them were resolved by a third reviewer. Data collected from the selected studies included first author, country, numbers of cases and controls, publication year, genotype frequencies of cases and controls, and Hardy-Weinberg equilibrium (HWE) test for controls.

Assessment of study quality

The authors assessed the methodological quality of each included article using the Newcastle-Ottawa quality assessment scale (NOS). An ultimate score of 6 stars or more was regarded as indicative of a high-quality study.

Statistical analysis

HWE was determined using Fisher's exact test by analyzing genotype distribution in controls. Correlation strength of *IL-4R* Q576R polymorphism with asthma risk was predicted based on the odds ratios (ORs) and the associated 95% confidence intervals (95% CIs), for allelic (G vs. A), heterozygous comparison (GA vs. AA), homozygous comparison (GG vs. AA), recessive (GG vs. GA + AA), and dominant gene models (GG + GA vs. AA) of both groups. The heterogeneity between studies was analyzed by the I^2 test; a random effects model was selected if $I^2 > 50\%$, indicative of heterogeneity, failing which the fixed effects model was adopted. One study was eliminated each time, to conduct sensitivity analysis; if the result of the analysis with one omitted study was beyond the 95% CI of combined analysis, the study was considered highly sensitive. To assess the possibility of publication bias, we visually inspected the funnel plot from Begg's test. Statistical analysis was completed with STATA (version 12.0; Stata Corporation, College Station, TX). A p-value < 0.05 (two-sided) was considered statistically significant.

Trial sequential analysis (TSA)

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 crossed the TSA boundary or entered the insignificance area, it demonstrated a sufficient level of evidence, and no further study was necessary. The TSA software (version 0.9.5.10 beta) was used for data processing [11].

Results

Study features

Studies related to the association between asthma risk and *IL-4R* Q576R polymorphism were identified from related databases. Figure 1 displays the study selection flowchart. Collectively, 12 case-control studies, involving 1553 patients and 1904 controls and conforming to the eligibility criteria, were enrolled [12–23]. Genotype distributions in each study conformed to HWE, with the exception of the study by Zhang *et al.* Every study was regarded as a separate dataset for the pooled analysis. The analysis involved eight and four studies on Asian and Caucasian populations, respectively. There were four studies on adults and two on children. Table I presents the features of the enrolled studies, and the allelic and genotypic distributions described in them. According to the NOS for case-control studies, the overall scores of the included studies ranged from six to eight stars. All studies were defined as high-quality.

Quantitative analysis

Table II presents primary results of the present meta-analysis and heterogeneities. In general, the *IL-4R* Q576R polymorphism did not show any significant relationship with asthma susceptibility using each genetic model (Figure 2: R vs. Q: OR = 1.25, 95% CI: 0.98–1.59; RQ vs. QQ: OR = 1.21, 95% CI: 0.98–1.49; RR vs. QQ: OR = 1.47, 95% CI: 0.80–2.71; recessive model: OR = 1.38, 95% CI: 0.80–2.40; dominant model: OR = 1.25, 95% CI: 0.98–1.60).

However, subgroup analyses of Asian and Caucasian populations, stratified by ethnicity, and that performed on adults and children, stratified by study population, revealed no obvious relationship between *IL-4R* Q576R polymorphism and asthma susceptibility.

Sensitivity analysis

Sensitivity analysis was performed to assess the reliability of our results, by ruling out one study each time. The results revealed that the combined ORs remained unaffected by every chosen study (Figure 3).

Publication bias

Funnel plot and Begg's test were used to assess publication bias (Figure 4). The results suggested low publication bias.

TSA results

This study conducted TSA to reduce the random errors and to fortify the robustness of our results. According to our results, the cumulative z-curve did not surpass RIS, and TSA and RIS thresholds were not crossed, indicating that the results were

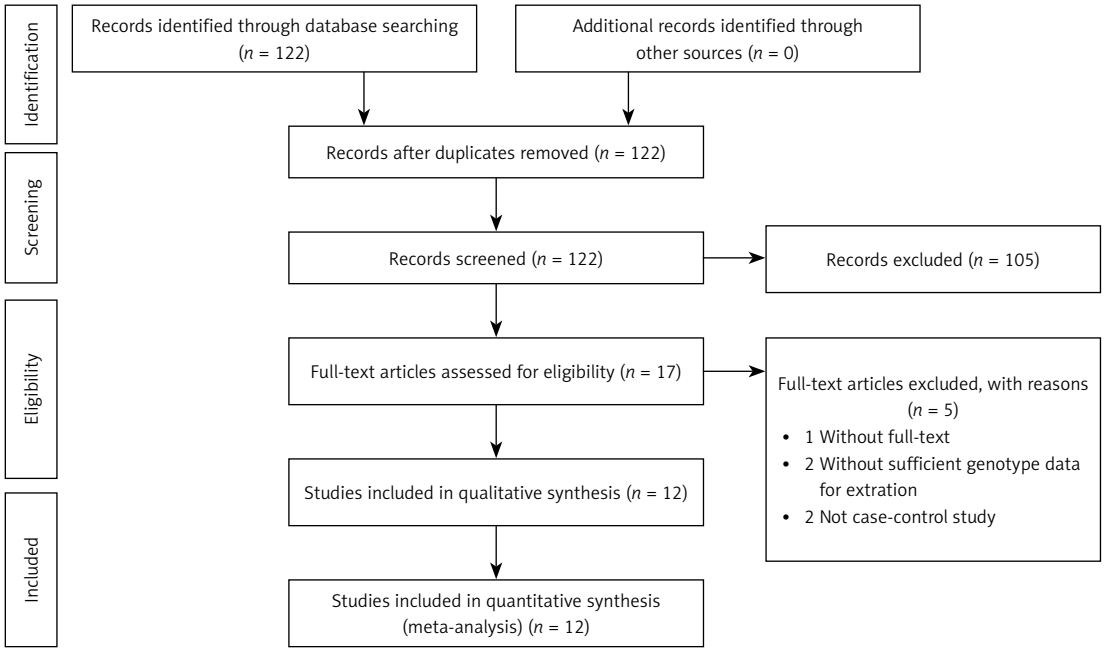

Figure 1. Flow diagram of included/excluded studies

Table I. Study selection and subject characteristics of studies included in meta-analysis

Author	Year	Area	Race	Study population	Cases	Controls	Allele for cases		Allele for controls		Genotypes for cases			Genotypes for controls			HWE
							R	Q	R	Q	RR	RQ	QQ	RR	RQ	QQ	Y/N (P)
Rosa-Rosa	1999	America	Caucasian	Adults	149	42	87	211	21	63	19	49	81	3	15	24	Y(0.76)
Risma	2002	America	Caucasian	Mixed	200	65	248	500	26	104	28	66	106	3	20	42	Y(0.76)
Cui	2003	China	Asian	Mixed	241	175	135	347	49	301	23	89	129	4	41	130	Y(0.72)
Isidoro-García	2005	Spain	Caucasian	Mixed	133	80	43	223	34	126	1	41	91	4	26	50	Y(0.79)
Zhang HB	2007	China	Asian	Mixed	352	114	103	601	27	201	8	87	257	0	27	87	Y(0.15)
Judith	2007	China	Asian	Mixed	285	291	89	481	109	473	4	81	200	9	91	191	Y(0.64)
Zhang WD	2007	Singapore	Asian	Adults	303	355	125	481	137	573	19	87	197	22	93	240	N(0.01)
Wu	2010	China	Asian	Children	252	227	77	427	63	391	8	61	183	4	55	168	Y(0.83)
Saleh	2014	Saudi Arabia	Asian	Mixed	162	194	88	236	62	326	12	64	86	5	52	137	Y(0.98)
Parisa	2015	India	Asian	Adults	100	50	45	155	30	70	6	33	61	5	20	25	Y(0.74)
Sun	2017	China	Asian	Adults	397	200	124	670	67	333	8	108	281	8	51	141	Y(0.23)
Afaf	2021	Egypt	Caucasian	Children	200	100	52	148	27	173	5	42	53	1	25	74	Y(0.48)

HWE – Hardy-Weinberg equilibrium, Y – yes, N – no.

Table II. Summary ORs and 95% CI of IL-4R Q576R polymorphism with asthma risk

Variables	N[a]	R vs. Q		RR vs. QQ		RQ vs. QQ		Dominant model		Recessive model	
		OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)		OR (95% CI)	
Total	12	1.25 (0.98–1.59)	R	1.47 (0.80–2.71)	R	1.21 (0.98–1.49)	R	1.25 (0.98–1.60)	R	1.38 (0.80–2.40)	R
Race:											
Asian	8	1.18 (0.89–1.57)	R	1.34 (0.66–2.73)	R	1.18 (0.92–1.52)	R	1.20 (0.90–1.62)	R	1.26 (0.67–2.37)	R
Caucasian	4	1.41 (0.84–2.37)	R	1.81 (0.48–6.85)	R	1.30 (0.95–1.78)	R	1.38 (0.82–2.30)	R	1.71 (0.50–5.88)	R
Study population:											
Adults	4	0.99 (0.83–1.19)	F	0.90 (0.57–1.42)	F	1.04 (0.82–1.31)	F	1.01 (0.81–1.26)	F	0.90 (0.57–1.41)	F
Children	2	1.55 (0.78–3.07)	R	1.81 (0.48–6.85)	R	1.50 (0.66–3.39)	R	1.60 (0.69–3.69)	R	2.47 (0.87–6.98)	F

[a]*Number of comparisons, CI – confidence interval, OR – odds ratio.*

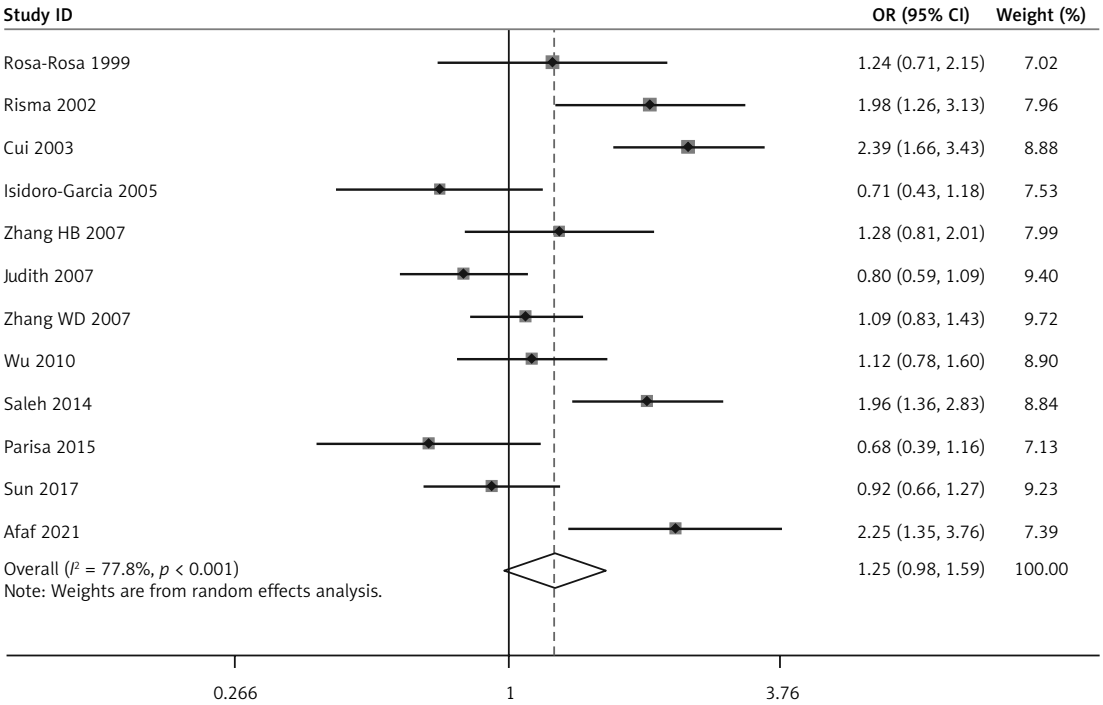

Figure 2. Forest plot for meta-analysis of the association between the IL-4R Q576R polymorphism and asthma risk

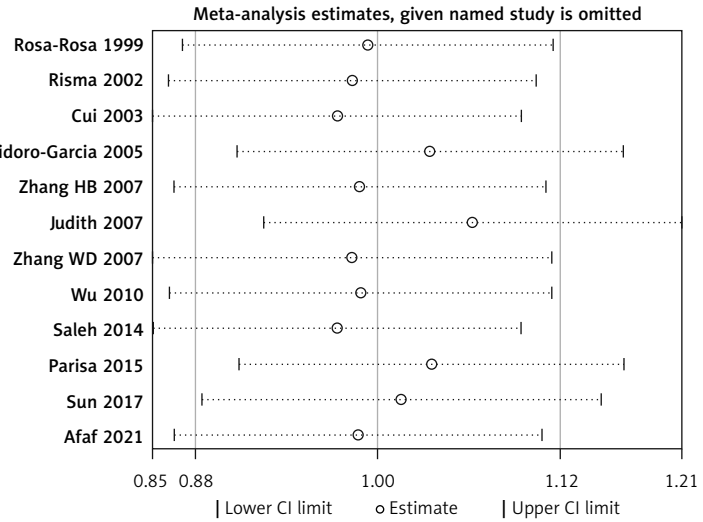

Figure 3. Sensitivity analysis of the association between the IL-4R Q576R polymorphism and asthma risk

unreliable and that more studies should be included (Figure 5).

Discussion

Asthma is a complicated, chronic disease of the respiratory system, and the airway inflammation induced by allergen facilitates its symptoms, such as cough, breathlessness, dyspnea, and wheezing [1]. Asthma has a complex pathogenic mechanism, with genetic susceptibility and poor glycemic control being instrumental to its occurrence. In the last decade, several epidemiological studies have examined the association between *IL-4R*

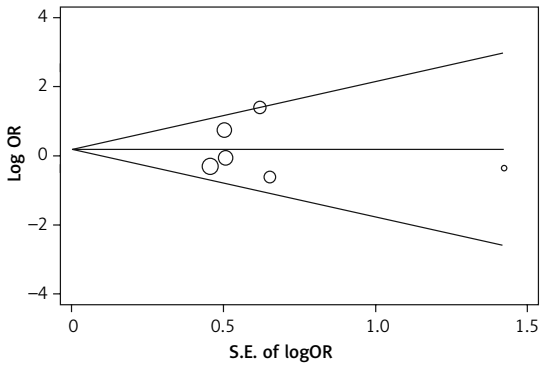

Figure 4. Begg's funnel plot analysis to detect potential publication bias for IL-4R Q576R polymorphism

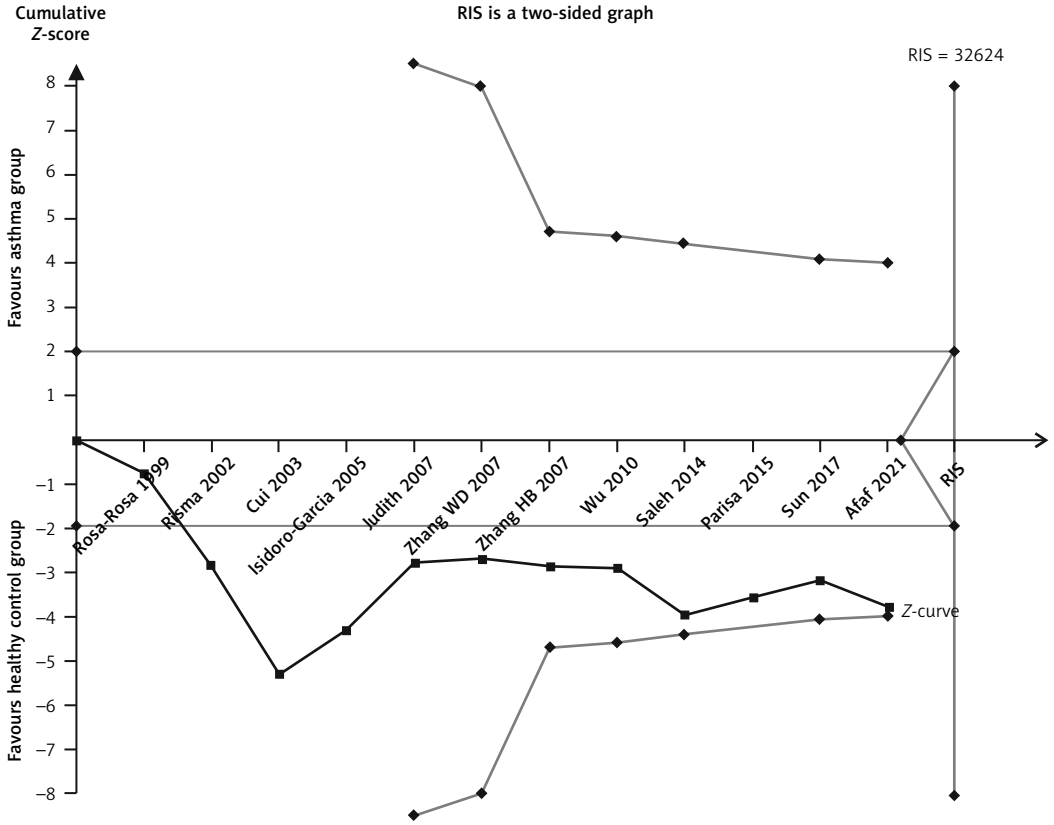

Figure 5. TSA analysis of the association between the IL-4R Q576R polymorphism and asthma risk

Q576R polymorphism and asthma susceptibility; however, they report inconsistent results. Studies with ethnic diversity, inadequate power, and the small effect size of the polymorphism on asthma susceptibility have made it even more complicated to interpret the results, rendering it impossible to unify these findings.

To overcome the heterogeneity that might confound the results, subgroup analyses based on study population and ethnicity were performed. According to the pooled data analysis of all genetic models and subgroup analyses, the *IL-4R* Q576R polymorphism was not identified as a risk factor for asthma. Sensitivity analysis was also carried out, which confirmed no significant association between T174M gene polymorphism and asthma susceptibility. The present meta-analysis showed no obvious potential publication bias. However, possible interpretations are available for such negative outcomes.

Firstly, many enrolled studies involved small sample sizes; our results had inadequate power to detect these minute, common effects from multifactorial studies that analyzed the genetic association [24]. Therefore, a larger sample size and inclusion of hereditary asthmatic patients could solve the above problem. Secondly, heterogeneities, possibly related to the differences in environmental traits and/or genetic constitution among different populations, sample characteristics selected (sex, age, diagnostic criteria, etc.), or study designs, could confer a possible negative influence on the results.

As several environmental factors and gene products have been found to increase asthma susceptibility, more attention should be devoted to the gene-environment and gene-gene interactions. Many recent studies have discussed the association between *IL-4R* Q576R polymorphism and additional potential genes. For instance, Cui *et al.* suggested that while *IL-4R* Q576R polymorphism alone was not related to asthma susceptibility, *IL-4R* Q576R/I75V gene-gene polymorphism combination showed an association with asthma predisposition [13]. In addition, Li *et al.* demonstrated that the synergistic effect of environmental factors, such as smoking and nurturing pets, along with *IL-4R* Q576R polymorphism, increases asthma susceptibility [25].

Some limitations should be noted in the present meta-analysis. To begin with, we conducted the present systematic review on the basis of unadjusted data, due to the unavailable genotype data analyzed according to the major confounders from the original studies, as well as the inconsistent results from articles analyzing diverse confounders. Secondly, there might be publication bias since the included studies were published in

the English language. Thirdly, the sample sizes of the studies included were small. TSA was used to check the reliability of conclusions in the present study. The cumulative Z-curve of *IL-4R* Q576R polymorphism did not reach the trial sequential monitoring boundary and required information size line, suggesting that larger sample, multi-ethnic research is required to verify the association. Finally, the present meta-analysis did not analyze the impact of gene-environment and gene-gene interactions.

In conclusion, *IL-4R* Q576R polymorphism may not increase asthma risk. More investigations are warranted to identify possible gene-environment and gene-gene interactions.

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Conflict of interest

The authors declare no conflict of interest.

References

1. Pawankar R. Allergic diseases and asthma: a global public health concern and a call to action. World Allergy Organ J 2014; 7: 12.
2. Makoui MH, Imani D, Motallebnezhad M, et al. Vitamin D receptor gene polymorphism and susceptibility to asthma: meta-analysis based on 17 case-control studies. Ann Allergy Asthma Immunol 2020; 124: 57-69.
3. Willemsen G, van Beijsterveldt TCEM, van Baal CGCM, et al. Heritability of self-reported asthma and allergy: a study in adult Dutch twins, siblings and parents. Twin Res Human Genet 2008; 11: 132-42.
4. Thomsen SF, van der Sluis S, Kyvik KO, et al. Estimates of asthma heritability in a large twin sample. Clin Exp Allergy 2010; 40: 1054-61.
5. Bierbaum S, Heinzmann A. The genetics of bronchial asthma in children. Respir Med 2007; 101: 1369-75.
6. de Benedictis FM, Attanasi M. Asthma in childhood. Eur Respir Rev 2016; 25: 41-7.
7. Nelms K, Keegan AD, Zamorano J, et al. The IL-4 receptor: signaling mechanisms and biologic functions. Annu Rev Immunol 1999; 17: 701-38.
8. 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.
9. 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.
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9.
11. Wetterslev J, Jakobsen JC, Gluud C. Trial sequential analysis in systematic reviews with meta-analysis. BMC Med Res Methodol 2017; 17: 39.
12. Elsaid A, Shoaib RMS, Badr SS, et al. Polymorphisms of interleukin 4 and interleukin 4 receptor genes and bronchial asthma risk among Egyptian children. Clin Biochem 2021; 93: 66-72.
13. Cui T, Wu J, Pan S, et al. Polymorphisms in the IL-4 and IL-4R [alpha] genes and allergic asthma. Clin Chem Lab Med 2003; 41: 888-92.
14. Isidoro-García M, Dávila I, Laffond E, et al. Interleukin-4 (IL4) and Interleukin-4 receptor (IL4RA) polymorphisms in asthma: a case control study. Clin Mol Allergy 2005; 3: 15.
15. Mak JCW, Ko FWS, Chu CM, et al. Polymorphisms in the IL-4, IL-4 receptor alpha chain, TNF-alpha, and lymphotoxin-alpha genes and risk of asthma in Hong Kong Chinese adults. Int Arch Allergy Immunol 2007; 144: 114-22.
16. Davoodi P, Mahesh PA, Holla AD, et al. 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: 675-80.
17. Risma KA, Wang N, Andrews RP, et al. V75R576 IL-4 receptor alpha is associated with allergic asthma and enhanced IL-4 receptor function. J Immunol 2002; 169:1604-10.
18. Rosa-Rosa L, Zimmermann N, Bernstein JA, et al. The R576 IL-4 receptor alpha allele correlates with asthma severity. J Allergy Clin Immunol 1999; 104: 1008-14.
19. Al-Muhsen S, Vazquez-Tello A, Alzaabi A. IL-4 receptor alpha single-nucleotide polymorphisms rs1805010 and rs1801275 are associated with increased risk of asthma in a Saudi Arabian population. Ann Thorac Med 2014; 9: 81-6.
20. Sun L, Xue W, Li J. Palm dermatoglyphs and interleukin-4 receptor polymorphisms in asthma. Biomed Rep 2017; 6: 21-6.
21. Wu X, 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.
22. Zhang H, Zhang Q, Wang L, et al. Association of IL4R gene polymorphisms with asthma in Chinese populations. Hum Mutat 2007; 28: 1046.
23. Zhang W, Zhang X, Qiu D, et al. IL-4 receptor genetic polymorphisms and asthma in Asian populations. Respir Med 2007; 101: 186-90.
24. Colhoun HM, McKeigue PM, Smith GD. Problems of reporting genetic associations with complex outcomes. Lancet 2003; 361: 865-72.
25. Li L, Li Y, Zeng XC, et al. Role of interleukin-4 genetic polymorphisms and environmental factors in the risk of asthma in children. Genet Mol Res 2016; 15. doi: 10.4238/gmr15048873.