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

Keywords
asthma, meta-analysis, IL-4R

Abstract
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Several articles 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 polymorphism’s small effect size that 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.

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Databases including Web of Science, PubMed, Google Scholar, CNKI and EMBASE were systematically searched for retrieving pertinent studies. Odds ratios (ORs) and the relevant 95% confidence intervals (CIs) were also calculated.

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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.

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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.
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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 figures 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, reporting a heritability of about 35–75% [3,4]. Therefore, to explore the possible role of genetic susceptibility in asthma pathogenesis, several studies have identified over 100 genes to this regard [5].

Interleukin-4 (IL-4) is implicated in B-cell isotype class switching to generate IgE and 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, like that of *CD23*, MHC class II, or *IgE* [7].
IL-4R gene has been identified as the potential asthma-related gene. As for IL-4Rα subunit, its encoding gene can be detected in chromosome 16p12.1 (GenBank Accession No. NM000418). IL-4R Q576R polymorphism (rs1801275) was initially detected by Hershey and colleagues, who discovered that 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, like chronic periodontitis and bronchiolitis [9].

Several studies have been carried out for examining 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 a potent statistical power for establishing this relationship. Thus, the present meta-analysis was conducted to assess this association.

Materials and methods

We carried out this meta-analysis, following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [10]. The 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

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 for identifying related articles.

Eligibility criteria

Qualified articles were recruited, following these inclusion criteria: (1) assessment of IL-4R Q576R polymorphisms as well as asthma susceptibility, (2) case-control studies, and (3) enough 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 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 I² test; a random effects model was selected if I² > 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. For assessing the possible 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 an 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 1 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 2 presents primary results of the present meta-analysis and heterogeneities. In general, 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 result, 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 were suggestive of a low publication bias.

TSA results
This study conducted TSA for diminishing the random errors and for fortifying our result robustness. 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 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 Q576R polymorphism and asthma susceptibility; however, they report inconsistent results. Studies with ethnic diversity, inadequate power, and the small effect size of polymorphism on asthma susceptibility have made it even more complicated to interpret the results, thus deeming it unnecessary to unify such 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, 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 for detecting 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 difference in environmental traits and/or genetic constitution among different populations, sample characteristics selected (like 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 the 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, Kimberly and colleagues 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 larger sample multi-ethnic research is required to verify the association. At last, the present meta-analysis did not analyze the impact of gene-environment and gene-gene interactions.

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

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Availability of data and materials**
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Competing interests**
The authors declare that they have no competing interests.

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**Authors' contributions**
NL is the first and corresponding author. YZ and NL conceived and designed the study. DH and HG acquired the data. TJ analyzed the data and interpreted the results. YZ and NL drafted the initial and final manuscripts. YZ and NL performed critical revisions of the manuscript. All authors read and approved the final version of the manuscript.

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**References**


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HWE: Hardy-Weinberg equilibrium; Y: yes; N: no.

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* Number of comparisons; CI: confidence interval; OR: odds ratio
Figure 1. The flow diagram of included/excluded studies.

Records identified through database searching (n=122)

Records identified through other sources (n=0)

Records after duplicates removed (n=122)

Records screened (n=122)

Records excluded (n=105)

Full-text articles assessed for eligibility (n=17)

Studies included in qualitative synthesis (n=12)

Studies included in quantitative synthesis (meta-analysis) (n=12)

Full-text articles excluded, with reasons (n=5)
1 Without full-text
2 Without sufficient genotype data for extraction
3 Not case-control study

Preprint
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.
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.