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Association between *CTLA4* +49A/G Polymorphism and Childhood Asthma Susceptibility: A Meta-analysis

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ABSTRACT

To investigate the association between single nucleotide polymorphism (SNP) of cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*) +49A/G locus and the risk of asthma in children by meta-analysis.

Six databases were searched for records on the association between *CTLA-4* +49A/G locus polymorphism and pediatric asthma. The retrieval time was from the establishment of each database to July 2024. Stata 15.0 software was applied, with the pooled OR and 95% CI calculated. Five genetic models (G/A, GA+AA/AA, G/GA+AA, GG/AA, and GA/AA) were analyzed.

Nine studies were included, covering 2133 Cases and 1572 controls. The combined results exhibited that the differences were all statistically significant under the allelic (OR, 0.53; 95% CI, 0.35-0.79), dominant (OR, 0.41; 95% CI, 0.24-0.71), recessive (OR, 0.60; 95% CI, 0.41-0.89), homozygous (OR, 0.38; 95% CI, 0.22-0.68) and heterozygous (OR, 0.52; 95% CI, 0.33-0.80) models.

The meta-analysis indicates that *CTLA-4* +49A/G SNP is related to susceptibility to pediatric asthma, and allele G and genotype GG+GA, GG, and GA correlated with a decreased risk of asthma.

Keywords: Asthma; Children; CTLA-4; Polymorphism

INTRODUCTION

Asthma is a chronic inflammatory disease of the airway involving various respiratory inflammatory cells, structural cells, and cell components.[1,2] Recurrent chest tightness, wheezing, dyspnea, and cough in asthmatic patients are typical symptoms of asthma.[3] Asthma is a common and frequent disease, which seriously threatens people's health, especially children's.[4] Asthma is difficult to get a radical cure and prone to recurrent attacks. The prevention and treatment of asthma have attracted great attention from governments of various countries and the World Health Organization (WHO).[5,6] Unfortunately, until now, the pathogenesis of childhood asthma is not well understood.

Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), also known as CD152 molecule, is an immunomodulatory molecule, a ligand of B7 molecule, belonging to the suppressor molecule of the

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immunoglobulin superfamily.[7] After binding its ligand, CTLA-4 induces T cells to participate in the negative regulation of immune response, that is, induces T cells to be unresponsive.[8] Mutations in *CTLA-4* are associated with susceptibility to diseases, such as diabetes, systemic lupus erythematosus, and asthma.[9-11] Nie et al's meta-analysis[11] in 2012 showed that *CTLA-4* +49A/G polymorphism influenced asthma risk. Zheng et 'al's[12] meta-analysis in 2018 reported that *CTLA-4* +49A/G locus genotype GG+GA could reduce the risk of asthma in children compared with genotype AA. However, Zheng et al[12] did not make further studies on other genotypic models of *CTLA-4* +49A/G polymorphism in children.

Therefore, based on previous studies, this study comprehensively searched online databases, using the meta-analysis method to systematically explore the relationship between *CTLA-4* +49A/G polymorphism and susceptibility to asthma in children, to provide evidence-based medical evidence for the pathogenesis of asthma. Unlike previous reviews, this study provides a comprehensive analysis of five genetic models and incorporates recent data.

MATERIALS AND METHODS

Literature Obtainment

We obtained records on asthma related to polymorphism from six databases up to July 2024, four English databases involving PubMed, Embase, Web of Science, and Cochrane Library, as well as two Chinese databases from China National Knowledge Infrastructure (CNKI) to China Wanfang. The main retrieval strategy was as follows: ("CTLA-4" OR "Cytotoxic T-lymphocyte-associated antigen 4") AND ("asthma" OR "Childhood asthma") AND ("polymorphism" OR "Single nucleotide polymorphism"). Moreover, we traced back relevant reviews or references. There were no restrictions on language. Two researchers searched simultaneously and finally checked to reach an agreement. If there was a disagreement, it was discussed and settled with a third researcher.

Five genetic models were analyzed to comprehensively evaluate the potential association patterns between polymorphism and asthma risk.

Literature Selection

Inclusion criteria: (1) Children with asthma were diagnosed according to the guidelines, younger than 18 years old; (2) The control group was non-asthmatic children; (3) *CTLA-4* +49A/G mutation; (4) The study design was a case-control study.

Exclusion criteria: (1) conference abstracts, reviews, letters, animal or cell experiments; (2) insufficient data; (3) low quality of trial.

Literature Quality Assessment

The bias risks of the included studies were assessed following Newcastle-Ottawa Scale (NOS) criteria.[13] The overall scores were nine, with a score of six or more rated as high quality. This meta-analysis was conducted in accordance with the PRISMA guidelines.

Data Extraction

Qualified studies were screened by two researchers, with a self-made data extraction form used for data collection. Any disagreement was resolved through discussion. Extracted information was as follows: first author, year, region, test method, age, number of cases in case group and control group, and frequency of *CTLA-4* +49A/G locus genotype GG, GA, and AA in case and control group. There were no language restrictions. For non-English articles (e.g., Chinese studies retrieved from CNKI/Wanfang), data were independently extracted and cross-checked by two bilingual investigators to ensure accuracy.

Statistical Analysis

Stata 15.0 statistical software was utilized, with the odds ratio (OR) and 95% confidence interval (CI) selected as effect sizes. Heterogeneity across the included literature was determined by Q test and I^2 statistics.[14] If $I^2 < 50\%$, and $p > 0.05$, the heterogeneity was considered not significant, so the data were processed with a model of fixed-effects. If homogeneity was not obvious ($I^2 \geq 50\%$, and $p \leq 0.05$), a model of random-effects model was selected. Sources of heterogeneity were investigated using subgroup analysis based on Hardy-Weinberg equilibrium (HWE). The funnel plot and Egger's test for the allele model were conducted to identify clue of publication bias. In addition, the meta-analysis was performed after each study was omitted, and the conclusions before and after exclusion were compared to verify the robustness of the conclusions. The following five genetic models were analyzed: (1) Allelic model (G/A); (2) Dominant model (GG + GA/AA); (3) Recessive model (GG/GA + AA); (4) Homozygous model (GG/AA); and (5) Heterozygous model (GA/AA).

RESULTS

Literature Identified Results

Nine articles[15–23] were included in this review (Figure 1). The basic characteristics of the included trials are illustrated in Table 1. The NOS scores of all included studies were more than six, which was considered to be of high quality.

Main Results of the Meta-analysis

Homogeneity Analysis

The I^2 of allelic (Figure 2), dominant, recessive, homozygous, and heterozygous (I^2 = 70.8%, p = 0.001) models (Figure 3A–D) was 92.8%, 84.9%, 84.4%, 82.0%, and 70.8%, respectively, suggesting high heterogeneity. Therefore, the random effects-model was used in each gene model.

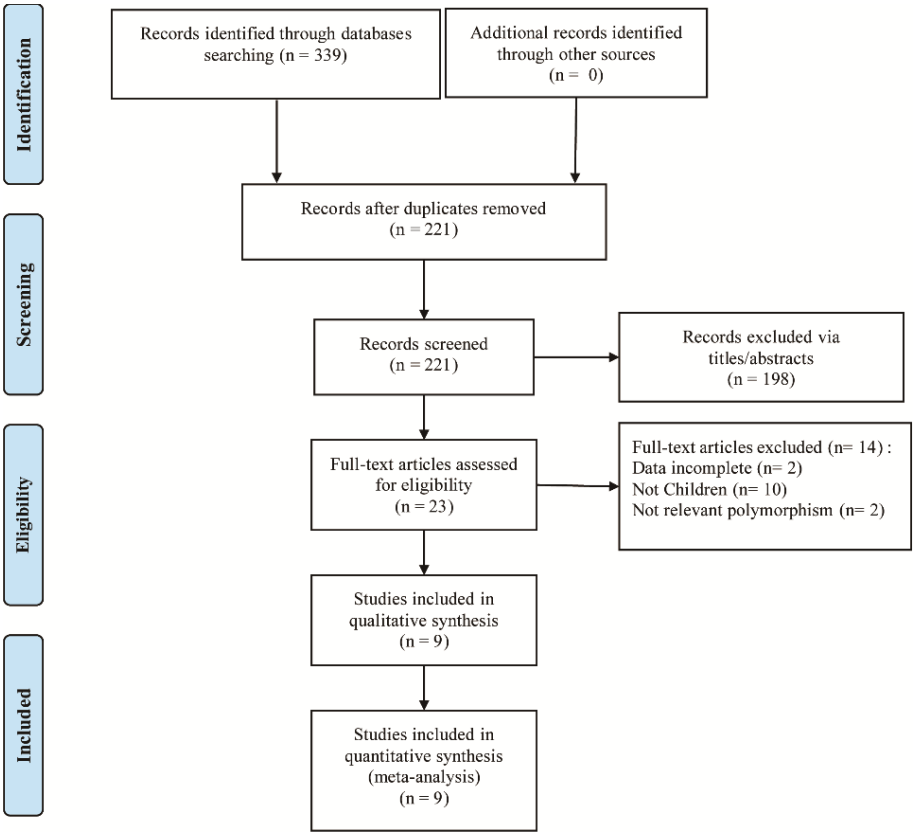

Figure 1. Literature search process, including identification, screening, eligibility and included

Comparison of Gene Models

The analysis results showed that, the ORs of the allelic (G/A, Figure 2), dominant (GG+GA/AA), recessive (GG/GA+AA), homozygous (GG/AA), and heterozygous gene model (GA/AA, Figure 3A–D) were 0.53 (95% CI: 0.35–0.79, p = 0.002), 0.41 (95% CI: 0.24–0.71, p = 0.001), 0.60 (0.41–0.89, p = 0.012), 0.38 (95% CI: 0.22–0.68, p = 0.001), and 0.52 (95% CI: 0.33–0.80, p = 0.003), respectively. All significances were observed.

Subgroup Analysis

In 8 studies[15–22], the control genotype frequency met HWE. Heterogeneity analysis of this subgroup showed a slight decrease in recessive (I^2 = 62.8%, p = 0.009) (Figure 3B), and GG/AA (Figure 3C) (I^2 = 68.2%, p = 0.002). In other genetic models, no significant decrease in heterogeneity was observed (Figure 2, Figure 3A, Figure 3D). Meta-analysis of the control group meeting HWE showed that OR of the GG/GA+AA was 0.81 (95% CI: 0.62–1.04, p = 0.103), without statistical significance. Nevertheless, the differences were still significant ORs of the allelic, dominant, homozygous, and GA/AA were OR = 0.65 (95% CI: 0.47–0.90, p = 0.009), 0.48 (95% CI: 0.28–0.81, p = 0.006), OR = 0.51 (95% CI: 0.32–0.81, p = 0.004), and 0.51 (95% CI: 0.32–0.82, p = 0.006), respectively, with significant difference.

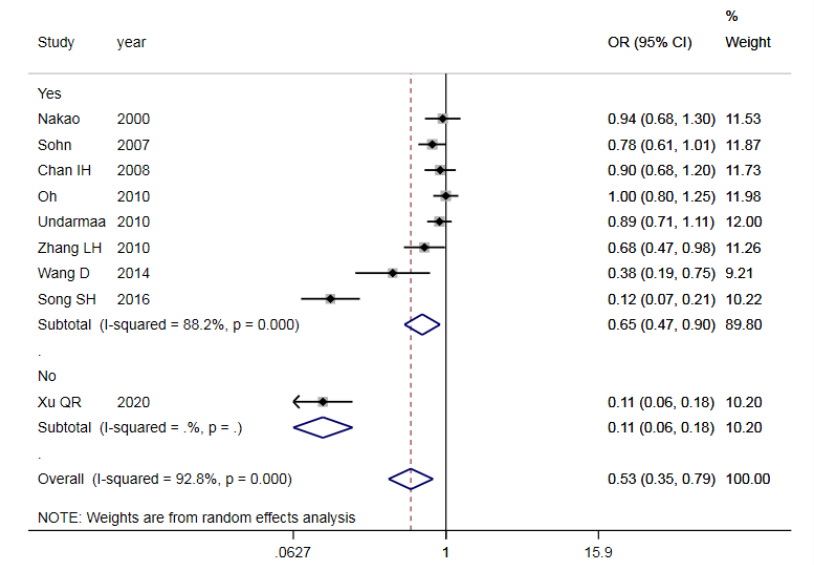

Figure 2. Forest plot of allele model at *CTLA-4* +49A/G associated with childhood asthma susceptibility

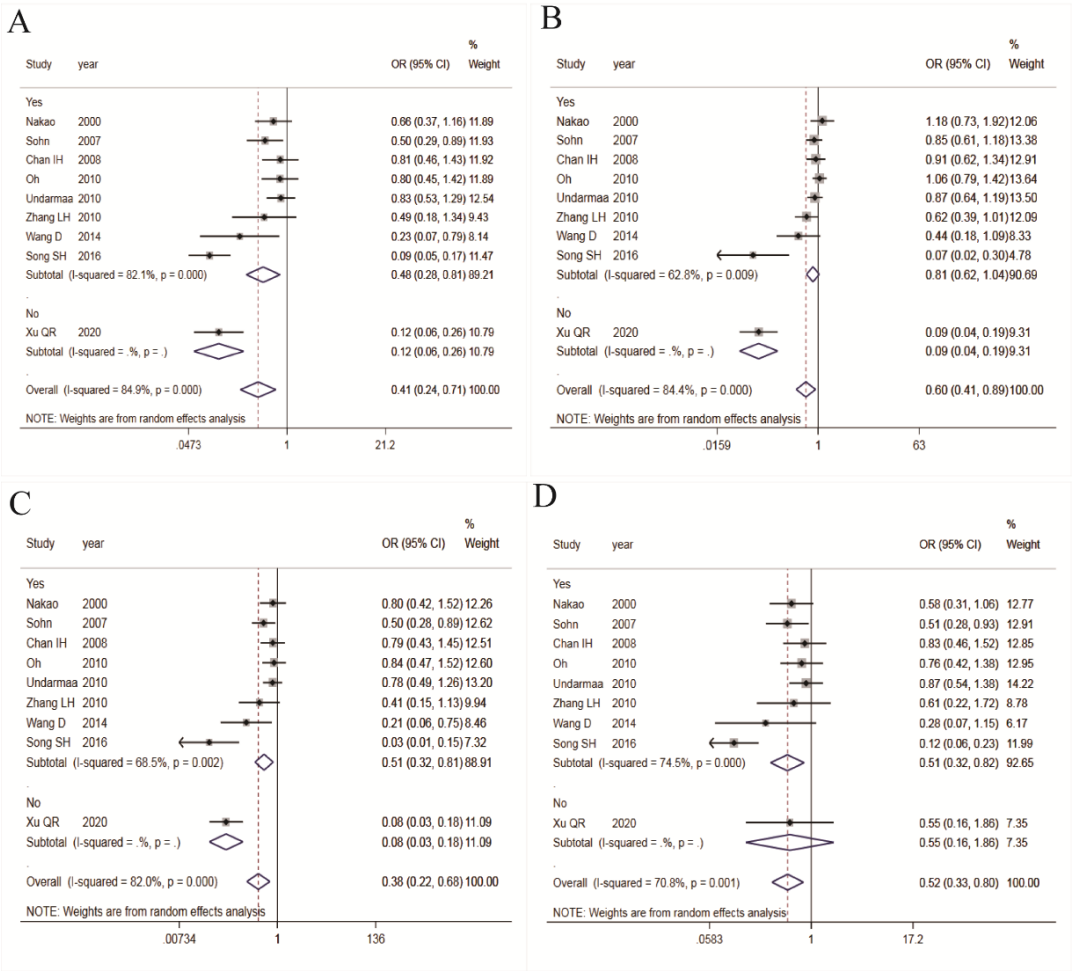

Figure 3. Forest plots of dominant (A), recessive (B), homozygous (C), and heterozygous (D) models at CTLA-4 +49A/G associated with childhood asthma susceptibility

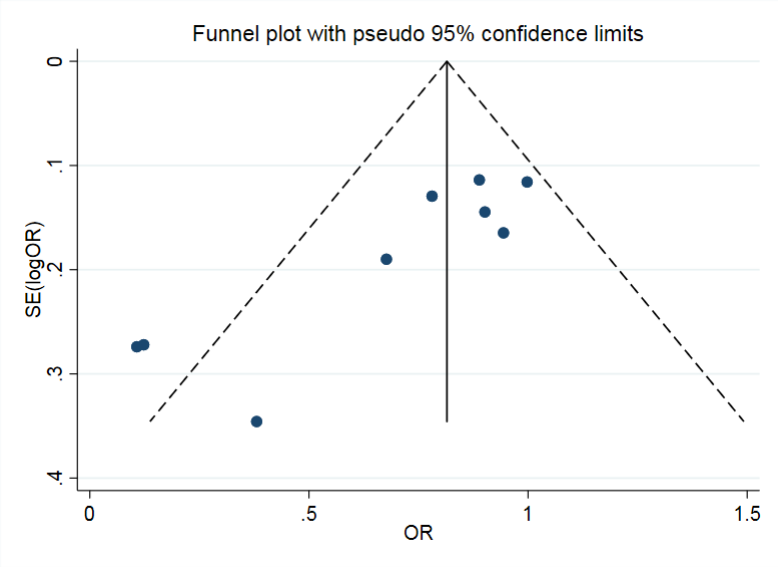

Figure 4. Funnel plot of allele model

DISCUSSION

Care should be taken when generalizing these findings to non-Asian populations. Asthma might be caused by the combination of environmental factors, immune factors, and genetic factors, resulting in chronic airway inflammation and airway remodeling. Asthma is the most common chronic disease in children, with increasing morbidity and mortality.[24] Due to the long course of the disease, it is prone to relapse, which causes a huge economic burden to the families of children and society. However, the pathogenesis of asthma remains to be elucidated. With the rapid development of genetics and molecular biology, more trials have focused on the studies of gene polymorphism in asthma. It has become urgent to find a cure for asthma.

This review displayed that *CTLA-4* +49A/G polymorphism was associated with the risk of childhood asthma. This was confirmed in five gene models. Moreover, the sensitivity analysis also suggested no significant change between the findings of the pooled analysis after the exclusion of each study and the results before the exclusion. In other words, the conclusions had good robustness. The stable results in sensitivity analysis (despite excluding individual studies) support the reliability of our findings despite the high heterogeneity. Zheng et al[12] meta-analysis reported that, compared with genotype AA, genotype GG+GA could reduce the risk of asthma in children. This is consistent with the conclusion of our meta-analysis. However, on the basis of Zheng et al meta-analysis,[12] our study included new high-quality literature.[22,23] Apart from the dominant gene model, we also conducted an in-depth analysis of the allele, recessive, homozygote, and GA/AA.

However, it is worth noting that the analysis of the G/A suggested a certain publication bias. Significant publication bias was detected in the G/A. While adjustment methods like "trim-and-fill" exist, they were not applied due to the high heterogeneity observed, which can render such adjustments unreliable. Thus, the potential for publication bias remains a limitation. In addition, we also found significant heterogeneity among the five gene models. After subgroup analysis according to HWE, there was no significant decrease in heterogeneity in the other gene models except for a slight decrease in the recessive and homozygous gene models. HWE might be one of the sources of heterogeneity. More future studies are needed to confirm the conclusions obtained in this meta-analysis.

This review had several limitations. First of all, only 9 studies were included, and the number of cases was small. Second, the identified studies were all in Asia, lacking Caucasian and African, etc., so it is doubtful whether the conclusions could be extrapolated to other races. Third, the analysis of each gene model showed high heterogeneity. Due to the lack of detailed stratified data (e.g., specific age groups) in the primary literature, we could not perform further subgroup analyses to identify sources of heterogeneity. Additionally, since all

included studies were from Asian populations, ethnicity-based subgroup analysis was not feasible. Although subgroup analyses were performed according to HWE, no obvious decrease was seen in heterogeneity. There might be other factors affecting heterogeneity. However, this study is the first meta-analysis to comprehensively investigate the association between *CTLA-4* +49A/G polymorphism and susceptibility to asthma in children, which has clinical significance. It is helpful to explore the pathogenesis of asthma in children, providing evidence for the prevention of asthma in children. It is important to note that all studies included in this meta-analysis were from Asian populations. Genetic backgrounds and environmental exposures (such as diet, air pollution, and specific allergens) differ significantly across regions. These environmental factors may interact with the *CTLA-4* gene, modifying its effect on asthma susceptibility. Therefore, our findings may not be directly extrapolatable to Caucasian or African populations. The total sample size (2133 cases and 1572 controls) was relatively small. This limited statistical power might prevent the detection of modest associations and restrict the feasibility of more granular subgroup analyses. This protocol was not pre-registered in PROSPERO.

In conclusion, our results support a potential association between the G allele and reduced asthma risk in Asian children. Nevertheless, these findings must be interpreted with caution due to the relatively small sample size and heterogeneity. Future research should prioritize large-scale, multi-ethnic studies to confirm these associations across different populations.

STATEMENT OF ETHICS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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