

Original Article

TLR4 +896A>G (Asp299Gly) polymorphism is not associated with asthma: a update meta-analysis

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Abstract: Some research reported that polymorphisms in the toll-Like receptor 4 may have influence on asthma risk. Here, we sought to estimate the effects of Toll-Like Receptor 4 (Asp299Gly) genes on asthma risk. Databases including PubMed and Chinese National Knowledge Infrastructure (CNKI) databases were searched to find relevant studies. The odds ratio (OR) with corresponding 95% confidence intervals (CIs) was performed. A total of 12 case-control studies were finally identified. This meta-analysis indicated that no significant association was found between TLR4 (Asp299Gly) genes and asthma risk (OR = 0.91, 95% CI = 0.71-1.12). In conclusion, our findings suggest that TLR4 +896A>G (Asp299Gly) polymorphism may not contribute to the risk of asthma.

Keywords: Toll-Like Receptor 4, single nucleotide polymorphism, asthma, polymorphism, meta-analysis

Introduction

Asthma is a chronic inflammatory airway disease, and is characterized by recurrent attacks of breathlessness and wheezing. The World Health Organization estimates that the global prevalence rates of doctor diagnosed asthma, clinical/treated asthma and wheezing in adults were 4.3%, 4.5%, and 8.6% respectively [1], and asthma occurs in all countries regardless of the level of development [2]. Asthma exhibits a complex etiology, resulting from interactions between genetic and environment factors. Studies indicate that asthma has significant genetic contributions, with heritability estimates varying between 35% and 95% [3]. Therefore, a complete understanding of the genetic risk factors for asthma is important to develop new treatments or prevention strategies. So far, a large number of studies have focused on this field [4].

Toll-Like Receptor 4 (TLR4) is a surface receptor expressed in macrophages and other cell types [5, 6], The receptor detects lipopolysaccharide (LPS) [7, 8] and plays an important role in the LPS-mediated activation of the innate immune system [9]. An A-to-G missense nucle-

otide substitution in the TLR4 gene (rs4986790; also reported as Asp299Gly) has been demonstrated to result in the reduction of cell surface expression of TLR4. Some researched revealed that TLR4 gene is not associated with asham [9, 10]. Meta analysis given the number of accumulated data can increase the statistical power and the precision of effect estimates.

The aim of the study is to obtain the relationship between Toll-Like Receptor 4 (Asp299Gly) genes polymorphism and asthma.

Materials and methods

Literature search

PubMed and Chinese National Knowledge Infrastructure (CNKI) databases (accessed October 22, 2014) were searched using the search terms: 'asthma' or 'asthmatic', 'Toll-Like Receptor 4' or 'TLR4', and 'polymorphism' or 'mutation' or 'variant'. We also searched the reference lists of the initially identified studies for any additional relevant studies. The reference lists of the identified articles were also examined by two independent reviewers. Disagreements of the results were resolved via consensus.

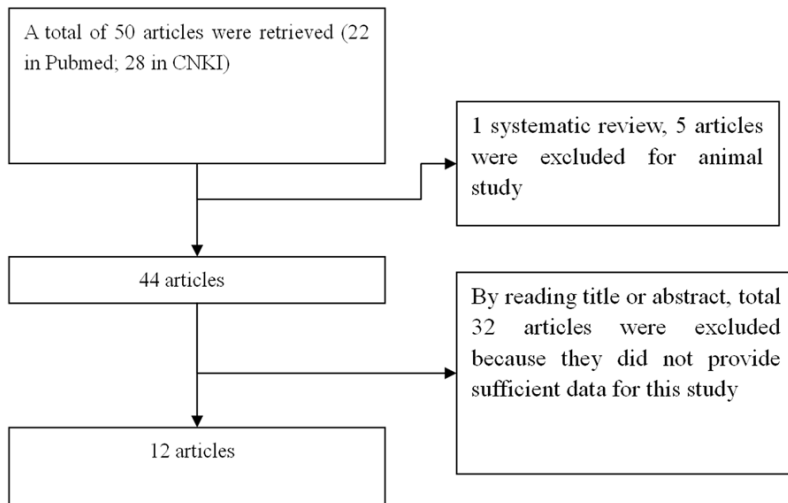


Figure 1. Flow diagram.

Inclusion and exclusion criteria

We included study met the following criteria: (1) the publication was a case-control; (2) the results of study offer sample information and related information that can calculate the sample size; (3) publication language was confined to English and Chinese; (4) genotype distribution of controls were in Hardy-Weinberg equilibrium (HWE). All case reports, reviews animal studies and studies with incomplete data were excluded. The articles in the final analysis were in English and Chinese.

Data extraction

Two reviewers independently extracted data from the relevant article. Disagreements were resolved through discussion and arbitration by another author. The following variable was extracted: first author, year of publication, country, age, controls, and the allele and genotype counts or frequencies of each SNP included.

Statistical analysis

The pooled odds ratios (ORs) and 95% confidence interval (CI) were used to assess the associations between the genetic variants of Toll-Like Receptor 4 and asthma risk. Heterogeneity assumption was evaluated by Q-test and I^2 test [11]. A significant Q-test ($P < 0.10$) indicated heterogeneity across studies. I^2 values were classified as low ($< 25\%$), moderate (25-50%), and high ($> 50\%$) heterogeneity,

respectively [12]. When there was no statistical heterogeneity, we used a fixed effects model (the Mantel-Haenszel method) [13]. The meta-analysis was performed using software Review Manager (RevMan, version 5.2, The Cochrane Collaboration), P value less than 0.05 was considered statistically significant.

Results

The primary search generated 50 potentially relevant articles. After reviewing these articles, 1 systematic review was excluded [14], 5

articles were excluded for animal study, and 32 articles were excluded because they did not provide sufficient data for this study. Thus, a total of 12 case-control studies were finally identified (**Figure 1**). The detailed characteristics of included studies and the genotype and allele distributions are summarized in **Table 1**. The forest plots are showed in **Figure 2**, and possible publication bias are showed in **Figure 3**.

Discussion

On the basis of 12 case-control studies involving 1838 asthma cases and 1764 controls, the present meta-analysis did not find a significant heterogeneity between-study, and significant association between the TLR4 (Asp299Gly) polymorphism and asthma.

Asthma is a common and complex pulmonary disorder. It was thought that asthma is a result of a combination of environmental factors and the accumulation of genetic variation. In future study we should explore the interaction of gene and environment on asthma.

There are some limitations to this review need to be taken into consideration when interpreting the findings. First, although multiple sources of literature were consulted and obvious publication bias was not detected, the effects of language bias and file drawer problem may impede the completeness of evidence. Second, the asthma phenotype was not consistently defined across studies, which may undermine

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Table 1. Characteristics of studies included

Author (years)	Country	Patients		Controls		HWE
		n-	AA/(AG/GG)	n	AA/AG/GG	
Adjers et al (2005) [15]	Finland	243	202/41	401	334/67	0.973
Carvalho et al (2008) [16]	The united kingdom	14	12/2	80	70/10	0.551
Hussein et al [17] (2012)	Egypt	500	434/66	251	223/28	0.851
J. Wang et al [10] (2014)	China	126	126/0	126	126/0	< 0.01
Lachheb et al [18] (2008)	Tunisia	210	209/1	224	223/1	< 0.01
Liu et al [19] (2005)	China	197	161/36	156	128/28	0.006
Sahin F et al (2014) [20]	Turkey	131	122/9	75	71/4	0.77
Smit et al [21] (2007)	Denmark	100	91/9	87	78/9	0.611
Voronko et al [22] (2011)	Russia	276	245/31	227	200/27	0.341
Yang et al [23] (2004)	The united kingdom	185	155/30	179	159/20	0.603
Yufeng Sun et al [24] (2013)	China	50	50/0	30	30/0	-
Zaborowski et al [25] (2011)	Poland	106	94/12	159	142/17	0.476

The heterogeneity among studies included was not significant ($Q = 2.22; P = 0.99, I^2 = 0\%$), This meta-analysis indicated that no significant association was found between TLR4 (Asp299Gly) genes and asthma risk (OR = 0.91, 95% CI = 0.71-1.12).

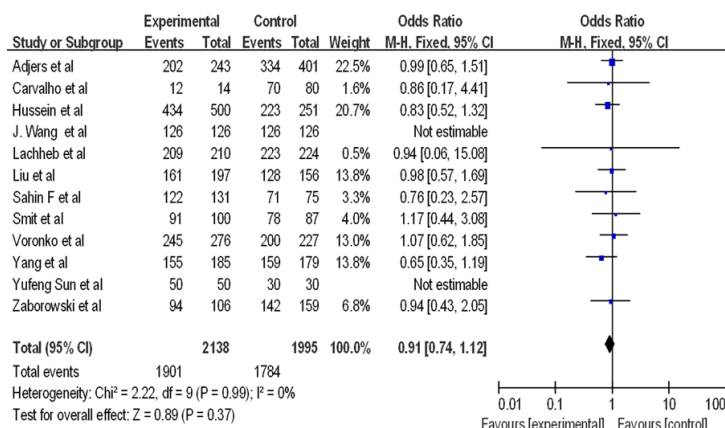


Figure 2. Forest plots of TLR4 +896 AG/GG versus AA genotypes for all studies included in the meta-analysis.

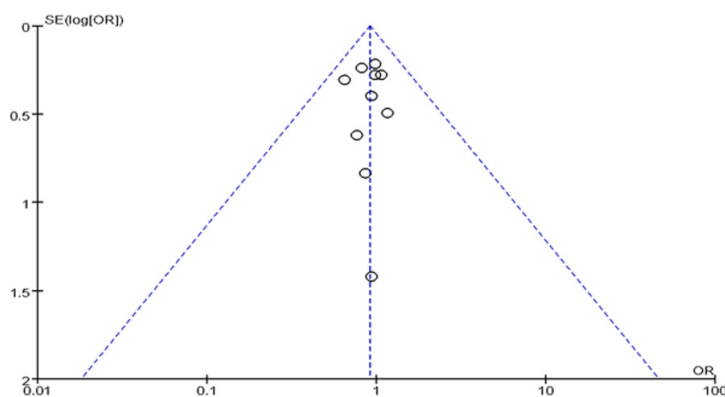


Figure 3. Forest plots of TLR4 +896 AG/GG versus AA genotypes for all studies included in the meta-analysis.

the validity of the met analysis. Likewise, the reference groups were not uniformly defined,

with some studies recruiting population based controls, while others recruiting hospital-based controls. Studies with controls in violation of HWE have been shown to give significantly different results from studies with controls conforming to HWE.

Conclusion

Our findings suggest that TLR4 +896A>G (Asp299Gly) polymorphism may not contribute to the risk of asthma.

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Disclosure of conflict of interest

None.

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