

Association of CD14 gene -159C/T polymorphism with allergic rhinitis risk: a meta-analysis

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Abstract The -159C/T polymorphism in the CD14 gene has been implicated in susceptibility to allergic rhinitis (AR), but results were conflicting. The aim of this study is to investigate the association between the CD14-159C/T polymorphism and the risk of AR. All eligible case-control studies published up to July 2013 were identified by searching PubMed, Web of Science and CNKI. Pooled odds ratio with 95 % confidence interval (95 % CI) was used to assess the strength of this association in fixed- or random-effects model. A total of seven case-control studies, including 887 cases and 889 controls, were selected. Overall, no significant association between the CD14-159C/T polymorphism and AR risk was found. Besides, stratified analysis with ethnicity and source of control also indicated that no significant association between CD14-159C/T and the risk of AR under all for genetic model was observed. This meta-analysis indicated that the CD14-159C/T polymorphism is not associated with AR risk.

Keywords CD14 · Polymorphism · Allergic rhinitis · Meta-analysis

Introduction

Allergic rhinitis (AR) is an atopic disease, which is characterized by episodes of rhinorrhea, sneezing, and itchy/

watery eyes, is strongly associated with IgE sensitization to grass and other pollens [1, 2]. The development of AR, as with other allergic conditions, pivots on the interplay between genetic predisposition and environmental exposures [3, 4]. Despite the latter play important roles in the development of atopy, there is a strong inherited susceptibility in the etiology of AR [5]. Variants in several genes have been identified as biologically plausible candidates for effects on AR, such as CD14 [6–9].

The CD14 gene is localized on chromosome 5q31.1, in a region shown to be linked to type 2 T lymphocyte (Th2) prevalent phenotypes, which encodes a receptor protein that binds to lipopolysaccharide (LPS), its primary ligand, and interacts with co-receptors toll-like receptor 4 (TLR4) and lymphocyte antigen 96 (LY96). CD14 is expressed on the surface of monocytes, macrophages, and neutrophils as membrane CD14 (mCD14) and in the serum as soluble CD14 (sCD14) and its expression may be partially regulated at the genetic level [10]. There are several polymorphism sites in the CD14 gene, and a well-studied common single nucleotide polymorphism (SNP) in the promoter region of CD14, -159C/T (rs2569190, also known as CD14 -260C/T), has been associated with increased CD14 expression in vitro and in the serum of children, and with altered serum IgE levels and skin test positivity in Chinese children [11].

Recently, the CD14-159C/T polymorphism is investigated extensively to the susceptibility of AR [12–18]. However, the results remain controversial. Some studies reported that there was no significant association between them [13, 17, 18]; while, other studies suggested CD14-159C/T polymorphism is significantly associated with AR [14, 16]. In addition, Han et al. [12] found that individual with TT genotype is associated with AR in Chinese adults. Conversely, Lu et al. [15] suggested that the allele C is

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related to AR. So, we conduct a meta-analysis to evaluate the association between the CD14-159C/T polymorphism and AR risk.

Materials and methods

Search strategy

We searched the PubMed, Web of Science and CNKI databases before July 22, 2013, by using the key subjects “allergic rhinitis”, “AR”, “genetic polymorphism”, “polymorphism”, “variant”, in combination with “cluster of differentiation 14”, “CD14”. Additional studies were identified by manual search of references of original articles on this topic. Search results were restricted to human populations and without language restrictions. If more than one geographic or ethnic heterogeneous group was reported in one report, each was extracted separately. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion criteria and exclusion criteria

Studies were included if they met the following criteria: (1) Studies clearly described the diagnoses of AR (2) studies that evaluated the association between the CD14-159C/T polymorphism and AR, (3) in a case–control study design, and (4) had detailed genotype frequency of cases and controls or could be calculated from the article text. While major exclusion criteria were: (1) case-only study, case reports, and review articles, (2) studies without the raw data of the -159C/T genotype of CD14 gene, and (3) studies that compared the CD14-159C/T variants in other atopic disease.

Data extraction and quality assessment

The two investigators independently extracted data and reached consensus on all of the items. If the two investigators generated different results, they would check the data again and have a discussion to come to an agreement. If they could not reach an agreement, a third expert was invited to the discussion. Data extracted from the selected articles included the first author’s name, year of publication, country of origin, ethnicity of study population, genotyping methods, source of control, number of cases and controls and HWE in controls (P value).

Statistical analysis

The risk of AR associated with the CD14-159C/T polymorphism was estimated for each study by odds ratios

(ORs) and 95 % confidence intervals (95 % CIs). Four different ORs were calculated: the dominant model (CT + TT vs. CC), the recessive model (TT vs. CT + CC), heterozygote comparison (CT vs. CC), and homozygote comparison (TT vs. CC). A χ^2 test-based Q statistic test was performed to assess the between-study heterogeneity [19]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P > 0.05$) or $I^2 < 50$ % indicated no heterogeneity across studies, the fixed effects model was used [20], or else the random-effects model was used [21]. Before the effect estimation of CD14 polymorphism in AR, we tested whether genotype frequencies of controls were in HWE using χ^2 test. To avoid the heterogeneity of ethnicity and sources of control, we performed stratification analyses on ethnicity and sources of control. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg’s funnel plot and Egger’s regression test [22, 23]. $P < 0.05$ was regarded as statistically significant. Statistical analysis was performed using the Cochrane Collaboration RevMan 5.1 (Copenhagen, 2008) and STATA package version 12.0 (Stata Corporation, College Station, Texas).

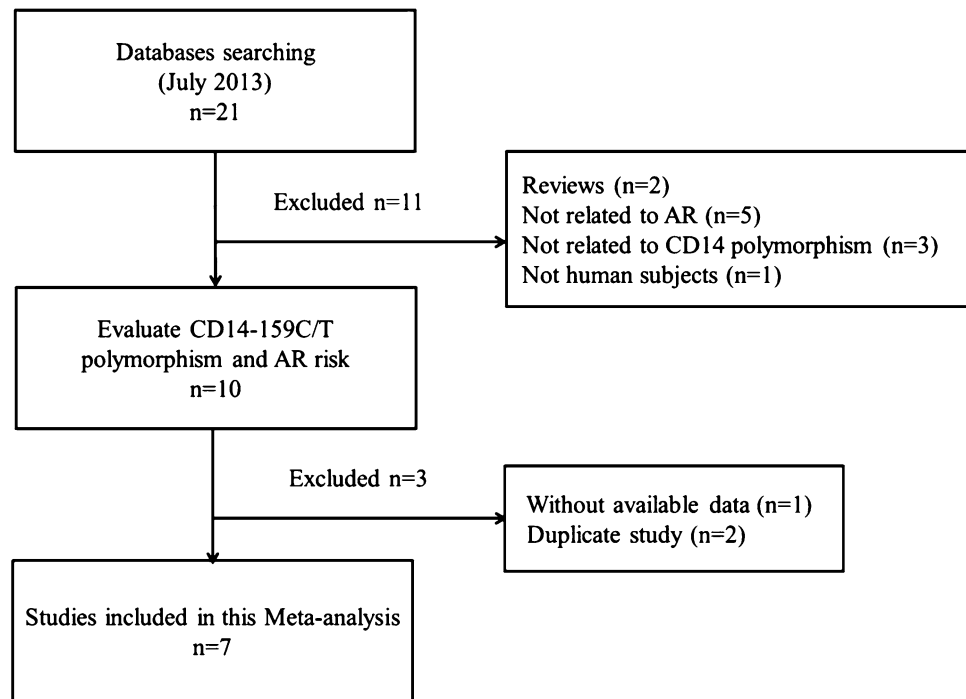
Results

Study characteristics

The search strategy retrieved 31 potentially relevant studies. According to the inclusion criteria, seven studies with full-text were included in this meta-analysis and 24 studies were excluded. The flow chart of study selection is summarized in Fig. 1. As shown in Table 1, there were seven case–control studies with 887 cases and 889 controls concerning CD14-159C/T polymorphism. Of seven case–control studies selected for meta-analysis, five studies were written in English, and two in Chinese; two ethnicities were addressed: six studies were conducted in Asians, and only one in Caucasians [17]. The distribution of genotypes in the controls was consistent with the Hardy–Weinberg equilibrium for all selected studies, except for three studies [12, 13, 17].

Quantitative data synthesis

Overall, no significant associations between the CD14-159C/T polymorphism and AR risk were found [dominant model: TT + CT vs. CC (OR = 0.79, 95 % CI: 0.47–1.32, $P = 0.37$), recessive model: TT vs. CT + CC (OR = 0.97, 95 % CI: 0.69–1.36, $P = 0.88$), CT vs. CC (OR = 0.97, 95 % CI: 0.63–1.51, $P = 0.90$), TT vs. CC (OR = 0.94, 95 % CI: 0.59–1.51, $P = 0.80$)] (Table 2;

Fig. 1 Flow chart showing study selection procedure**Table 1** Characteristics of studies included in the meta-analysis

Study	Year	Country	Ethnicity	Genotyping methods	Source of control	Case				Control				P_{HWE}
						Total	CC	CT	TT	Total	CC	CT	TT	
Han [12]	2010	China	Asian	TaqMan	PB	92	14	40	38	72	10	45	17	0.03
Hu [13]	2010	China	Asian	TaqMan	HB	300	50	140	110	300	65	128	107	0.02
Kang [14]	2006	Korea	Asian	PCR-RFLP	HB	164	44	83	37	160	38	85	37	0.43
Lu [15]	2006	China	Asian	PCR-RFLP	HB	60	28	19	13	40	6	16	18	0.44
Micheal [16]	2011	Pakistan	Asian	PCR-RFLP	PB	110	21	64	25	120	40	49	31	0.05
Sengler [17]	2003	German	Caucasian	PCR-RFLP	PB	80	16	46	18	119	26	72	21	0.02
Takeuchi [18]	2005	Japan	Asian	PCR-RFLP	PB	81	19	40	22	78	14	37	27	0.83

PB population-based, HB hospital-based, HWE Hardy–Weinberg equilibrium, P_{HWE} was calculated by goodness-of-fit χ^2 test, $P_{HWE} < 0.05$ was considered statistically significant, PCR-RFLP polymerase chain reaction–restriction fragment length polymorphism

Fig. 2). That is to say, the CD14-159C/T genotype distribution between AR and control group was no significant difference.

In the subgroup analysis by ethnicity, similar results were observed in Asian populations [dominant model: TT + CT vs. CC (OR = 0.91, 95 % CI: 0.54–1.52, $P = 0.71$), recessive model: TT vs. CT + CC (OR = 0.93, 95 % CI: 0.63–1.35, $P = 0.69$), CT vs. CC (OR = 0.95, 95 % CI: 0.56–1.59, $P = 0.84$), TT vs. CC (OR = 0.88, 95 % CI: 0.51–1.51, $P = 0.64$)] (Table 2); while only one study focused on Caucasians, indicated that the CD14-159 SNP might not play a major role in the development of AR in German children.

In the stratified analysis based on source of control, no significant association was found both in hospital-based and population-based populations (Table 2).

Test of heterogeneity

There was significant heterogeneity for overall comparisons (dominant model: TT + CT vs. CC: $P < 0.0001$, $I^2 = 79$ %, recessive model: TT vs. CT + CC: $P = 0.03$, $I^2 = 56$ %, CT vs. CC: $P = 0.009$, $I^2 = 65$ %, TT vs. CC: $P = 0.01$, $I^2 = 63$ %). In the subgroup analysis by ethnicity and source of control, the heterogeneity still exists, indicating that the different ethnicities and control selection

Table 2 Stratified analysis of the CD14-159C/T polymorphism and AR risk

Variables	N ^a	CT + TT vs. CC		TT vs. CT + CC		CT vs. CC		TT vs. CC	
		OR (95 % CI)	P ^b	I ² (%)	OR (95 % CI)	P ^b	I ² (%)	OR (95 % CI)	P ^b
Total	7	0.79 (0.47, 1.32)	<0.0001	79	0.97 (0.69, 1.36)	0.03	56	0.94 (0.59, 1.51)	0.01
Ethnicity									
Asian	6	0.91 (0.54, 1.52)	0.002	74	0.93 (0.63, 1.35)	0.03	61	0.88 (0.51, 1.51)	0.01
Caucasian	1	0.38 (0.20, 0.70)	N/A	N/A	1.35 (0.67, 2.74)	N/A	N/A	1.39 (0.57, 3.38)	N/A
Source of control									
PB	4	0.85 (0.38, 1.90)	0.002	81	1.15 (0.69, 1.92)	0.07	57	1.21 ^c (0.79, 1.85)	0.37
HB	3	0.70 (0.30, 1.63)	0.002	84	0.80 (0.48, 1.35)	0.06	64	0.93 (0.66, 1.30)	0.002

^a Number of comparisons^b Test for heterogeneity^c Fixed-effects model was used when the *P* value for heterogeneity test was > 0.05, otherwise random-effects model was used

OR odds ratio, CI confidence interval

may not be the source of heterogeneity; while we found that the heterogeneity, after successively removing two studies by Han et al. and Lu et al. was effectively removed or decreased (Table 2).

Sensitivity analyses

We examined the influence of these studies on the pooled OR by repeating the meta-analysis while excluding one study at a time. The estimated pooled odds ratio did not change (data not shown), indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (Fig. 3). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: *P* = 0.117, CT vs. CC: *P* = 0.138, TT vs. CC: *P* = 0.315, recessive model: *P* = 0.680).

Discussion

Genetic epidemiologic studies of single nucleotide polymorphism, if large and unbiased, can provide evidence of the association between candidate gene and disease risk. Many candidate genes were reported to be associated to AR risk, such as CD14 gene, and there have been reported polymorphisms associated with AR risk in these candidate genes. For CD14 gene, several polymorphisms have been described and investigated [24, 25], and, of these, the C-159T promoter polymorphism has been the most extensively studied in atopic disease. In vitro studies using transient transfection assays in CD14 expressing monocytic cells showed that the C-159T polymorphism increases transcription by lowering the affinity of the CD14 regulatory region for Sp3 [26], a factor known to inhibit the activity of a number of promoters [27]. In clinical studies, the C-159T TT genotype has been associated with higher circulating sCD14, a lower mean number of positive skin tests, and lower serum IgE levels in British and American white populations [28, 29]. Conversely, the CC genotype has been associated with higher levels of total serum IgE and a higher number of positive skin tests in a population from the Netherlands [30], and the C allele has been associated with atopy, specifically to moulds, in a Czech population [31].

The -159C/T polymorphism in CD14 gene has been investigated for the association with many diseases, such

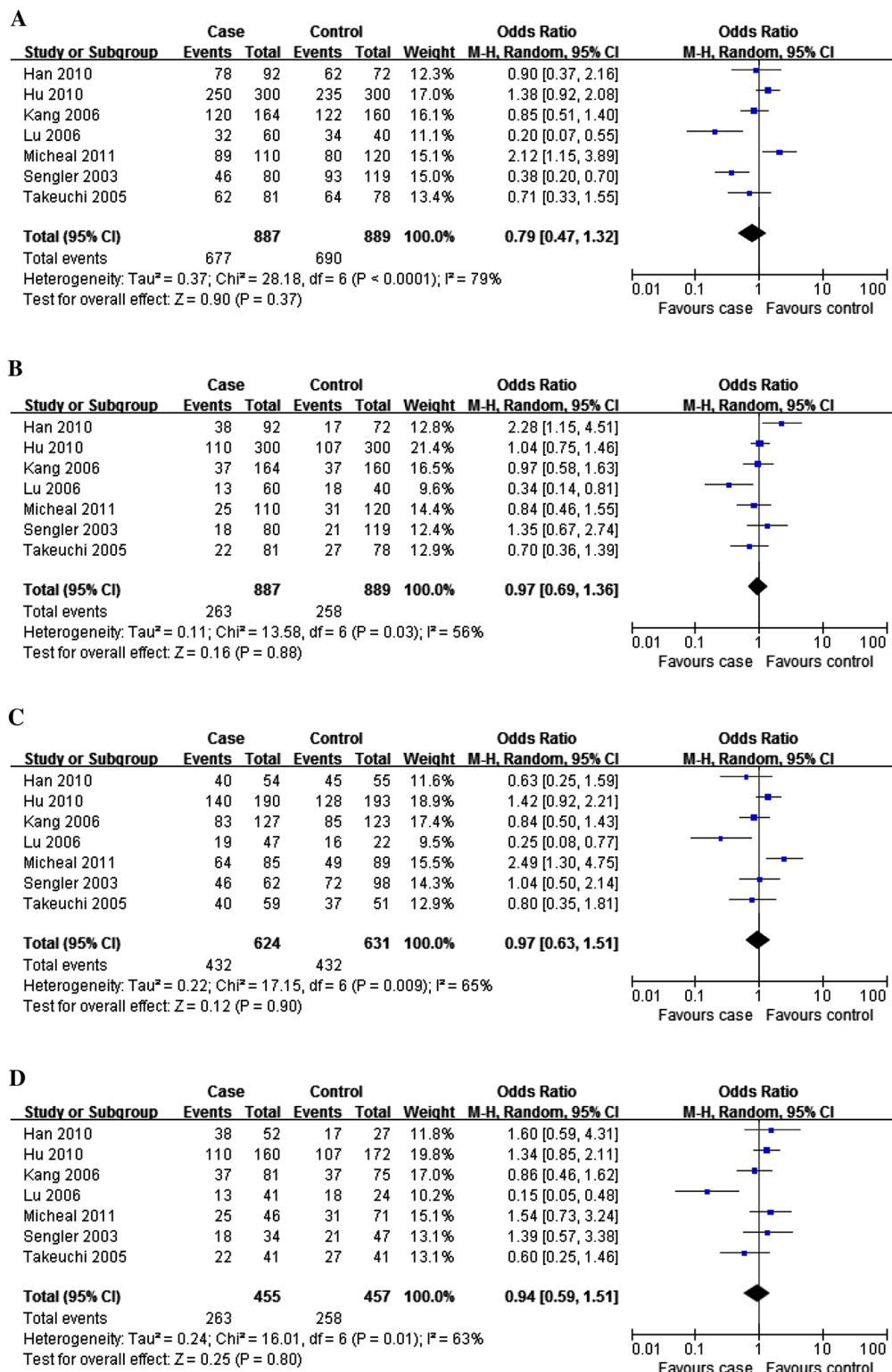


Fig. 2 Meta-analysis of the association between CD14-159C/T polymorphism and susceptibility to AR. **A** dominant model. **B** recessive model. **C** CT vs. CC. **D** TT vs. CC

as asthma [32], periodontitis [33], inflammatory bowel disease [34], alcoholic liver disease [35], systemic lupus erythematosus [36], tuberculosis [37], coronary heart

disease [38], cerebrovascular diseases [39], and ischemic heart disease [40]. To our knowledge, this is the first meta-analysis which comprehensively assessed the association

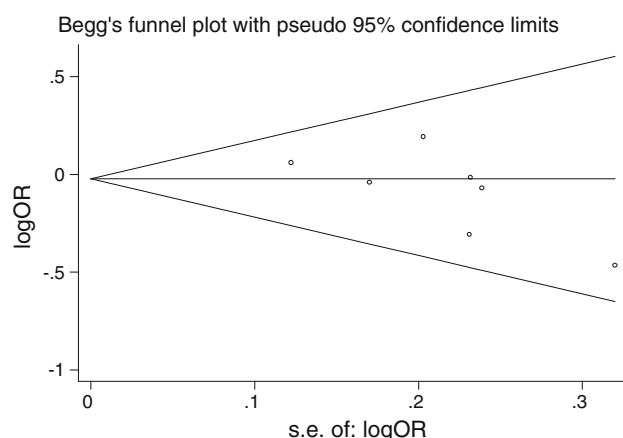


Fig. 3 Begg's funnel plot for publication bias. (dominant model) Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line mean effect size

between CD14-159C/T polymorphism and AR risk. The current meta-analysis including seven case-control studies and 4,124 subjects were conducted to explore the association of the CD14-159C/T polymorphism with AR. Overall, no evidence has indicated that the CD14-159C/T polymorphism was associated with the susceptibility to AR. In the subgroup analysis by ethnicity and source of control, similarly, we did not detect any association between CD14-159C/T polymorphism and AR risk in Asians, hospital-based and population-based populations. The results seem to contradict the observations of functional studies of CD14, which had suggested that CD played a pivotal role in the development of AR. However, as AR was a complicated multi-genetic disease, the discrepancy may be due to different genetic backgrounds and environmental exposures, gene-gene and gene-environmental interaction, and other factors (such as age, gender).

Heterogeneity is a potential problem when interpreting the results of all meta-analysis. In this study, heterogeneity was found in overall comparisons using all four genetic models. Ethnicity was an important reason for this heterogeneity. Individuals from different ethnicities may have diverse genetic backgrounds and environmental factors, and consequently, the same polymorphism may play different roles in different populations. Therefore, we performed stratified analysis by ethnicity, whereas, the heterogeneity still exists; Furthermore, the source of the controls was another factor that contributed to heterogeneity, so we conducted subgroup analysis by it, the heterogeneity markedly decreased in population-based population under TT vs. CC, while, in other genetic models, the heterogeneity also exists. Then sensitivity analyses were conducted by excluding one study successively, the estimated pooled OR changed quite little, strengthening the results from this meta-analysis, while

removing one study by Han et al. or Lu et al. the heterogeneity was effectively removed or decreased. The results above suggest that control selection and particular study may contribute to the heterogeneity observed in the meta-analysis. In addition, life style, environment background and other unknown factors may also be the source of heterogeneity.

Some limitations of this meta-analysis should be addressed. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, significant heterogeneity was found in some models, which may lead the failure to confirm marginal associations. Third, our results were based on unadjusted estimates, while lacking of the information for the date analysis may cause serious confounding bias. Fourth, individual study deviation from HWE might reflect the presence of genotyping errors, population stratification and selection bias in the controls. In this meta-analysis, three in seven studies were not in HWE, so the result should be cautiously interpreted. Fifth, the majority of data used for the meta-analysis are from the East Asian population.

In conclusion, this meta-analysis suggested that the CD14-159C/T polymorphism is not associated with AR risk. However, considering the limitations in our study, large and well-designed studies are warranted to validate our findings.

Conflict of interest We declare that we have no conflict of interest.

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