The Relationship Between Padi4 -94G/A Polymorphism and Rheumatoid Arthritis: A Meta-analysis in Multi Ethnic Groups

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Abstract

Background: A number of studies have reported the association between peptidylarginine deiminase 4 (PADI4) -94G/A polymorphisms and rheumatoid arthritis (RA) risk in different populations, however, the results remained inconclusive.

Objecitve: We therefore aim to address this association by performed an updated meta-analysis in multi ethnic groups.

Methods: The PubMed and Chinese related databases were searched up to January 2019. The strength of association between PADI -94G/A polymorphism and RA susceptibility was assessed with odds ratios (ORs) and 95% confidence intervals (CIs).

Results: A total of 22 studies with 14514 RA cases and 21138 controls were finally included in the analysis. Six ethnic groups such as China, Japan, USA, UK, Sweden and Spain were contained. In the overall population, it revealed that PADI -94G/A polymorphism was significantly associated with an increased risk of RA. In the subgroup analyses by ethnicity, significant association was found in China as well as in Japan and USA.

Conclusions: This meta-analysis demonstrates that the PADI4 -94G/A polymorphisms may represent a significant risk factor for RA in China, in Japan and USA. Further studies are needed to clarify this finding, since most available studies were conducted among Chinese and Japanese in this study.

Background

Rheumatoid arthritis (RA) is one of the most common chronic systemic inflammatory diseases that cause joint destruction. In the United States, the overall prevalence of definite RA among adults is approximately 10 per 1,000 (1.0%); rates for women are approximately 2.5 times higher than rates for men [1]. As the world's population ages and the proportion of people over the age of 60 increases, the prevalence of RA has also increased. The etiology and pathogenesis of RA is not fully understood. However, it has been hypothesized that the greatest impact of increased prevalence of RA is not due to the outcome of aging, but may be associated with genetic and environmental predisposing factors [2–4]. Peptidylarginine deiminase 4 (PADI4) -94G/A (rs2240340) has been identified as one of the RA susceptibility single nucleotide polymorphism, the results, however, are not frequently reproducible. In retrospect, individual studies with small sample sizes that are known to have low statistical power and yielded poor replication record. Moreover, this lack of reproducibility might also stem from discrepant lifestyle backgrounds. In order to reduce the influence of the diverse backgrounds, we performed a meta-analysis to assess the relationship between PADI − 94G/A polymorphism and RA risk in multi ethnic groups respectively.

Materials And Methods

Search strategy and selection criteria

We performed the meta-analysis according to the guidelines of the PRISMA group. The PubMed and Chinese related databases were searched for studies on the relationship between PADI − 94G/A polymorphism and the risk of RA. The search keywords were (PADI4 or peptidylarginine deiminase 4 or -94G/A) and rheumatoid arthritis. The last search was updated on January, 2019. Additional records were identified by manual searching. Inclusion criteria: (1) studies on the association between PADI − 94G/A polymorphism and RA, (2) independent cohort or case-control studies in humans, (2) providing sufficient genetypes data in cases and controls. Exclusion criteria: (1) duplicate literatures, (2) incomplete data, (3) no controls, (4) review articles.

Data Extraction

Two reviewers extracted the data independently based on the inclusion criteria. Disagreements were resolved by a discussion. The following information was collected from each qualified study: first author's name, publication year, ethnicity, sample size, and available genotype information from PADI − 94G/A polymorphism. Titles and abstracts of all potentially relevant articles were screened firstly. Full articles were then scrutinized if the title and abstract were ambiguous.

Statistical analysis

The strength of association between PADI − 94G/A polymorphism and RA susceptibility was assessed with odds ratios (ORs) and 95% confidence intervals (CIs). The distributions of genotypes in controls were tested by Hardy-Weinberg equilibrium (HWE) using the Chi-square test. Four comparisons were performed: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Statistical heterogeneity was measured by Chi-squarebased Q-test. A fixed effects model was used when there was no heterogeneity among these studies; otherwise, the random-effects model was used. The significance of the pooled ORs were evaluated by a Z-test. Sensitivity analysis was performed by comparing the results of fixed-effects model and random-effects model. Begg's funnel plot and Egger's linear regression test were conducted to assess the publication bias. All statistical analyses were conducted using the Stata, version 12 (StataCorp LP, College Station, TX). A P value less than 0.05 was considered to be statistically significant.

Results

Description of included studies

Figure 1 illustrates the literature search process with a flow chart. Two hundred and twenty-five articles which examined the association between PADI polymorphisms and RA were identified. According to the inclusion and exclusion criteria, eighteen article (22 studies) with PADI − 94G/A and RA [5–22] were

finally included in the analysis. The publication year of involved studies ranged from 2003 to 2014. In total, 14514 RA cases and 21138 controls were included in this meta-analysis. Six ethnic groups such as China, Japan, USA, UK, Sweden and Spain were included in our study. The pooled analysis was not performed for Sweden and Spain due to only one study respectively. The characteristics of these included studies are provided in Table 1.

Table 1
Characteristics of studies included in the meta-analysis

References	publication year	Ethnicity	RA number	Controls number	HWE in controls	
					χ^2	*P*
Cui et al [5]	2007	China	92	116	1.32	0.250
Feng et al [6]	2009	China	115	106	3.14	0.076
Shi et al [7]	2010	China	112	97	1.76	0.185
Chen et al [8]	2011	China	378	204	0.93	0.334
Cui et al [9]	2011	China	134	140	1.81	0.179
Xu et al [10]	2011	China	130	130	1.95	0.162
Cheng et al [11]	2012	China	324	695	0.10	0.751
Liu et al [12]	2012	China	90	90	0.27	0.602
Li et al [13]	2013	China	192	288	1.43	0.231
Du et al [14]	2014	China	1216	1021	4.54	0.033
Suzuki et al [15]	2003	Japan	822	646	0.05	0.829
Ikari et al [16]	2005	Japan	1201	944	0.01	0.916
Takata et al [17]	2008	Japan	946	503	0.53	0.466
Harney et al [20]	2005	UK	100	94	0.00	0.989
Burr et al [21]	2010	UK	3732	3039	1.29	0.256
Burr et al [21]	2010	UK	1859	10599	0.01	0.929
Plenge et al [18]	2005	USA	895	748	3.59	0.058
Costenbader et al [19]	2008	USA	217	214	0.12	0.729
Costenbader et al [19]	2008	USA	164	165	0.83	0.362
Costenbader et al [19]	2008	USA	49	47	0.19	0.661
Plenge et al [18]	2005	Sweden	1498	858	2.26	0.133
Martinez et al [22]	2005	Spain	248	394	0.18	0.669

Meta-analysis Results

The primary results of this meta-analysis on the association between PADI − 94G/A polymorphism and RA risk are shown in Table 2. In the overall population, it revealed that PADI − 94G/A polymorphism was significantly associated with an increased risk of RA in four models (Table 2, Fig. 2).

Table 2
Association of the PADI − 94G/A polymorphism and RA susceptibility.

Analysis model		n	OR_r(95%CI)	OR_f(95%CI)	P_h
A vs. G	Total analysis	22	**1.16 (1.09–1.24)**	**1.10 (1.07–1.14)**	0.000
	China	10	**1.24 (1.14–1.35)**	**1.24 (1.15–1.34)**	0.371
	Japan	3	**1.28 (1.17–1.39)**	**1.28 (1.18–1.38)**	0.342
	UK	3	1.00 (0.95–1.05)	1.00 (0.95–1.05)	0.510
	USA	4	**1.18 (1.05–1.32)**	**1.18 (1.05–1.32)**	0.414
AA vs. GG	Total analysis	22	**1.33 (1.18–1.51)**	**1.21 (1.14–1.30)**	0.001
	China	10	**1.49 (1.28–1.73)**	**1.49 (1.28–1.73)**	0.495
	Japan	3	**1.64 (1.39–1.94)**	**1.64 (1.39–1.94)**	0.396
	UK	3	1.03 (0.93–1.13)	1.03 (0.93–1.13)	0.458
	USA	4	**1.35 (1.08–1.69)**	**1.35 (1.08–1.69**	0.498
AA vs. GG + GA	Total analysis	22	**1.15 (1.07–1.24)**	**1.13 (1.07–1.20)**	0.229
	China	10	**1.19 (1.04–1.36)**	**1.19 (1.04–1.35)**	0.916
	Japan	3	**1.42 (1.22–1.65)**	**1.42 (1.22–1.65)**	0.613
	UK	3	1.06 (0.96–1.17)	1.06 (0.97–1.15)	0.326
	USA	4	1.18 (0.97–1.45)	1.18 (0.97–1.45)	0.537
AA + GA vs. GG	Total analysis	22	**1.12 (1.13–1.40)**	**1.14 (1.09–1.20)**	0.000
	China	10	**1.50 (1.25–1.81)**	**1.45 (1.29–1.62)**	0.042
	Japan	3	**1.36 (1.21–1.54)**	**1.36 (1.21–1.53)**	0.360
	UK	3	0.97 (0.90–1.04)	0.97 (0.90–1.04)	0.489
	USA	4	1.22 (0.99–1.52)	**1.27 (1.08–1.50)**	0.272

ORr: Odd ratio for random-effects model; ORf: Odd ratio for fixed-effects model; P_h: *P* value for heterogeneity test.

Padi − 94g/a Polymorphism With Ra In China And Japan

Ten studies including 2783 cases and 2887 controls identified an association between the PADI − 94G/A polymorphism and RA risk in China [5–14], as well as three studies including 2969 cases and 2093 controls in Japan [15–17]. It revealed that PADI − 94G/A polymorphism was significantly associated with an increased risk of RA both in China and Japan among all analysis models (Table 2, Figs. 2).

Padi − 94g/a Polymorphism And Ra In Usa

Four studies including 1325 cases and 1174 controls identified an association between the PADI − 94G/A polymorphism and RA risk in USA [18–19]. Meta-analysis revealed that PADI − 94G/A polymorphism was significantly associated with an increased risk of RA in allelic contrast, in homozygotes and dominant models (Table 2, Figs. 2).

Padi − 94g/a Polymorphism And Ra In Uk

Three studies determined the relationship between PADI − 94G/A polymorphism and RA risk in UK [20–21]. The total sample size for patients with RA and controls was 5691 and 13732, respectively. It revealed that PADI − 94G/A polymorphism was not associated with RA in UK (Table 2, Figs. 2).

Sensitivity Analysis And Publication Bias Diagnosis

To evaluate the sensitivity of this meta-analysis, we compared the consistency between fixed-effects model and random-effects model. All the analysis results were not materially altered except the dominant model in USA (Table 2). Hence, the pooled results in this meta-analysis are relatively stable and credible. The Begg's funnel plot and Egger's test were performed to evaluate the publication bias. As showed in Fig. 3, the shape of the funnel plot did reveal obvious asymmetry. Similarly, the Egger's test showed that there was obvious publication bias in all the included studies (t = 4.29, $p = 0.000$, Fig. 4).

Discussion

Although the multifactorial nature of RA is well known, genetic factors are considered to be strong determinants of these diseases, thus encouraging researchers to search for the responsible genes. PADI4 has been implicated in the pathogenesis, activity and severity of RA [23–24]. Since the first positive association between PADI − 94G/A and RA was reported in a Japanese population [15], a number of studies have reported the association between PADI − 94G/A polymorphisms and RA risk in different populations. Till now, there are several published meta-analyses regarding PADI4 -94G/A polymorphisms and RA risk [25–30]. Of these, two meta-analyses reported that there was significant association between PADI4 -94G/A polymorphism and RA risk both in Asian and European population [26, 28], while two meta-analyses reported that there was significant association only in Asian individuals [27, 29]. However, only one meta-analysis was conducted in a separate ethnic group [30]. Therefore, we performed this meta-

analysis to assess the relationship between PADI − 94G/A polymorphism and RA risk in multi ethnic groups respectively.

Our meta-analysis involved 22 studies with 14514 RA cases and 21138 controls. The results showed that a significantly elevated risk of RA was associated with all variants of PADI4 -94G/A in the overall analysis. In the subgroup analyses by ethnicity, significant association was found in China as well as in Japan and USA. Compared with the previous meta-analyses [25–30], the current study involved more research in multi ethnic groups. And the effects of gene-environment interactions with respect to RA risk were also conducted by each separate ethnic group analysis. The sensitivity analysis confirmed the reliability and stability of the meta-analysis. Therefore, the findings from our meta-analysis provide a strong evidence for the association between PADI4 -94G/A polymorphism and RA in the three contries. It also indicated that the relationship between PADI4 -94G/A polymorphism and RA might be susceptible in different ethnicity.

Nevertheless, there are several limitations to this meta-analysis. First, because the papers searched in our study were limited to those openly published, it is possible that some non-published literature that may meet the inclusion criteria were missed. Second, non-English/Chinese articles and databases were not reviewed in our meta-analysis, thus might introduce some bias. Third, due to the relative small sample size of some studies or lack of necessary information, we did not perform further subgroup analyses. Finally, publication bias existed in our analysis, which indicated that other language studies should be included.

In conclusion, this meta-analysis demonstrates that the PADI4 -94G/A polymorphisms may represent a significant risk factor for RA in China, in Japan and USA. Ethnicity seems to play an important role in the genetic association of the disease. Further studies are needed to clarify this finding, since most available studies were conducted among Chinese and Japanese in this meta-analysis.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The authors agree to share the data and materials of this paper.

Competing interests

The authors report no conflicts of interest.

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None.

Authors' contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. CJ designed the study and wrote the protocol and performed research/study, JP contributed important reagents, JP and CJ managed the literature searches and analyses, JP undertook the statistical analysis and wrote the first draft of the manuscript.

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Figures

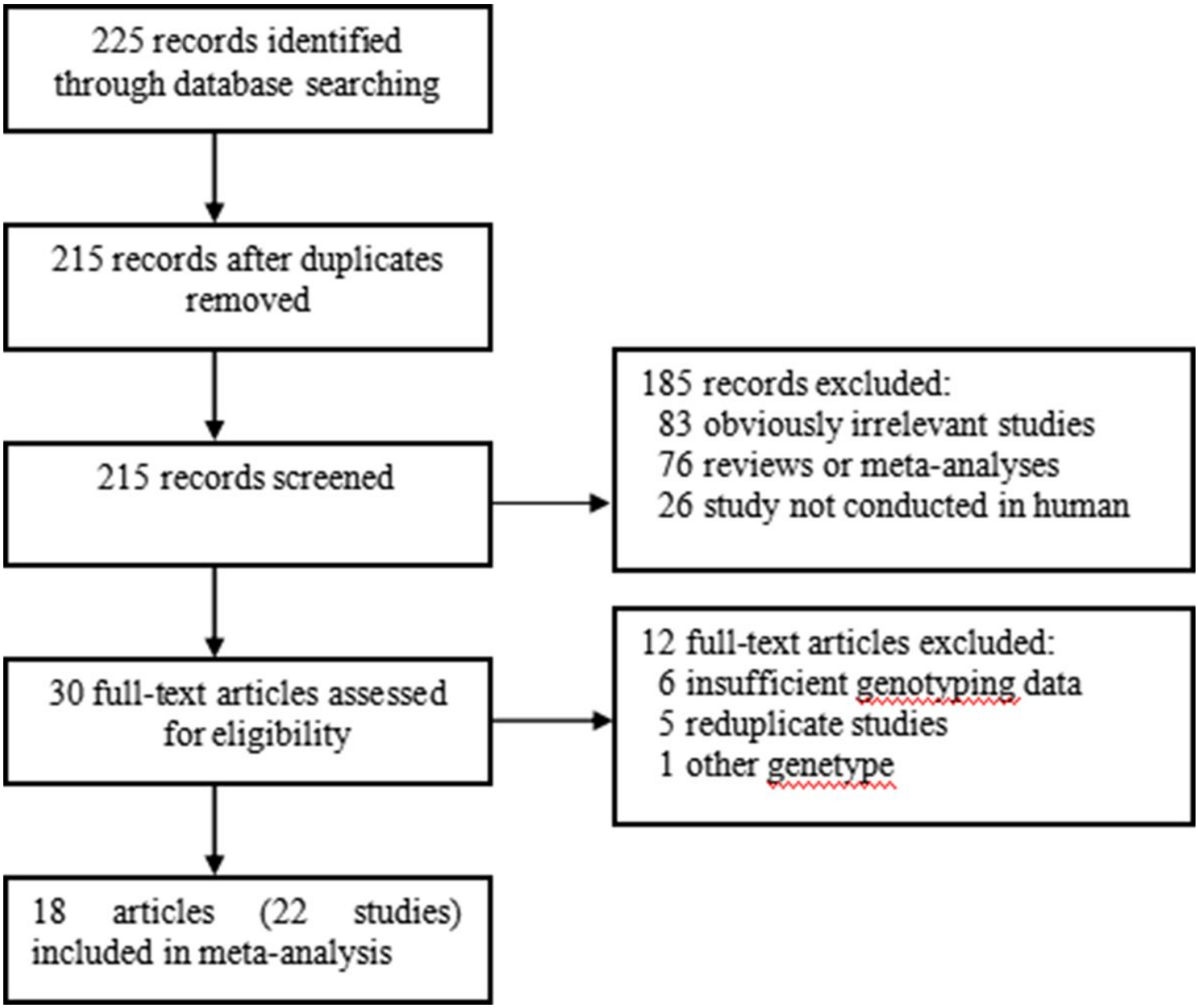

Figure 1

Flow diagram of the literature search.

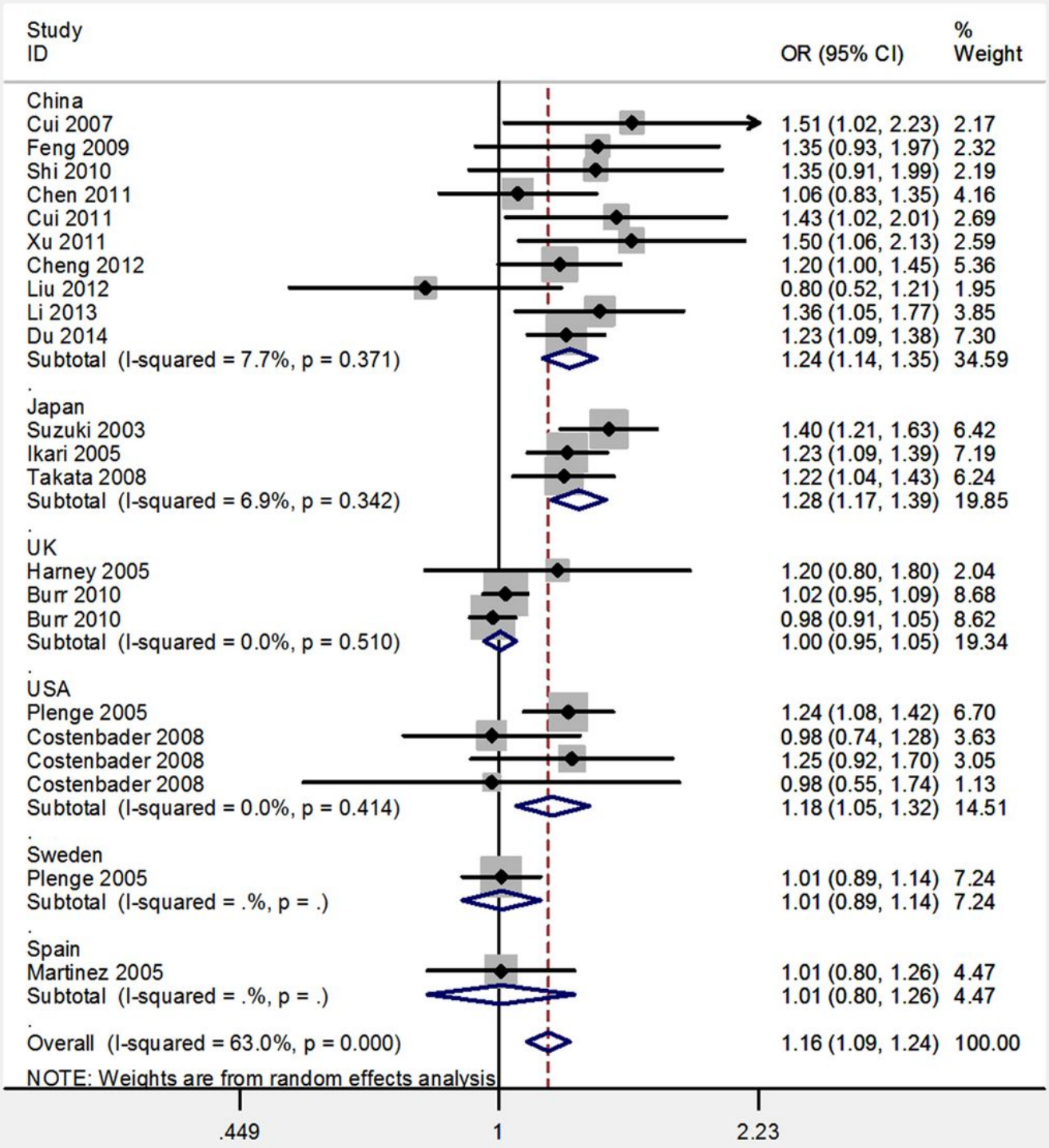

Figure 2

The forest plots of all selected studies on the association between PADI -94G/A polymorphism and RA susceptibility under allele model.

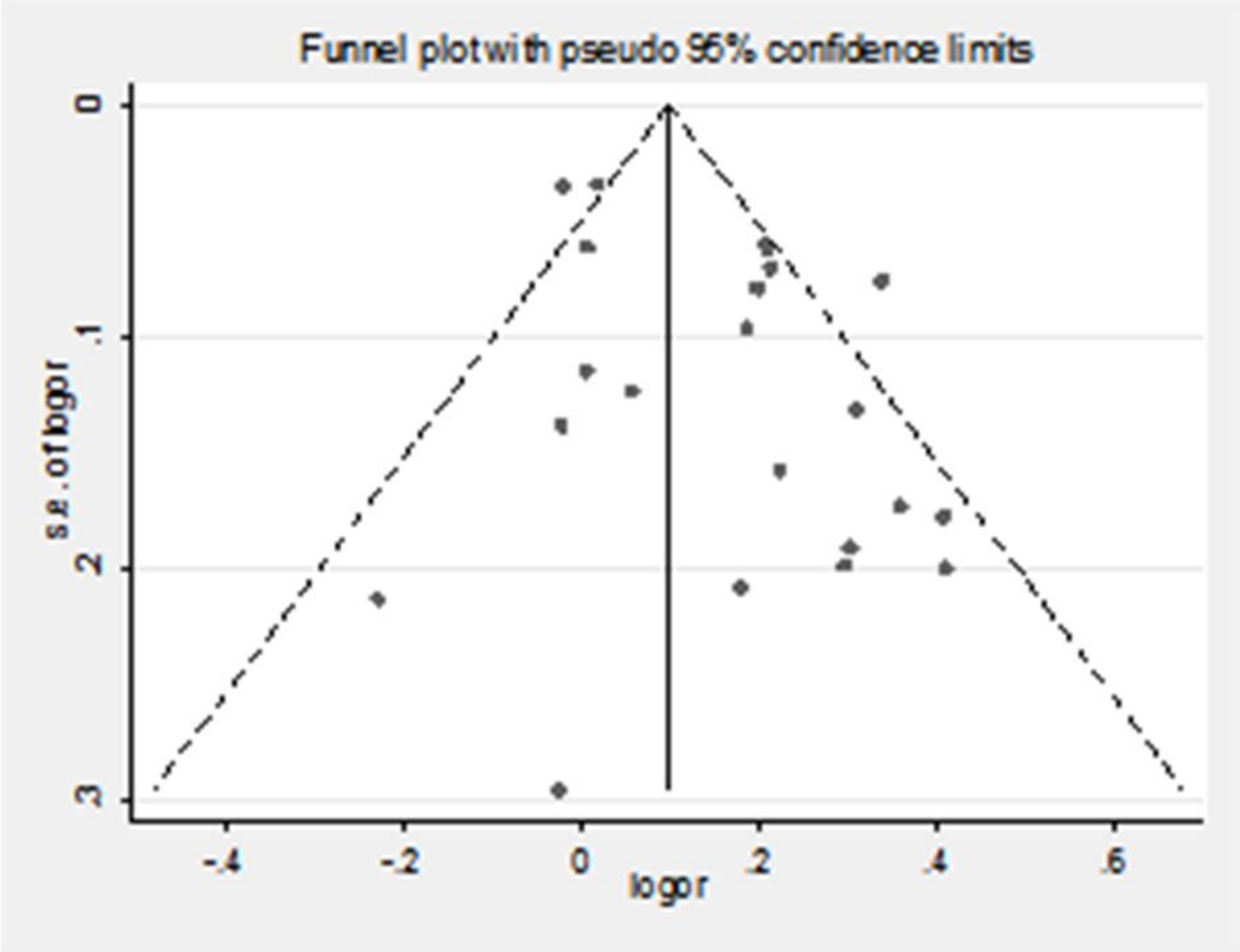

Figure 3

Publication bias assessment with Begg's funnel plot.

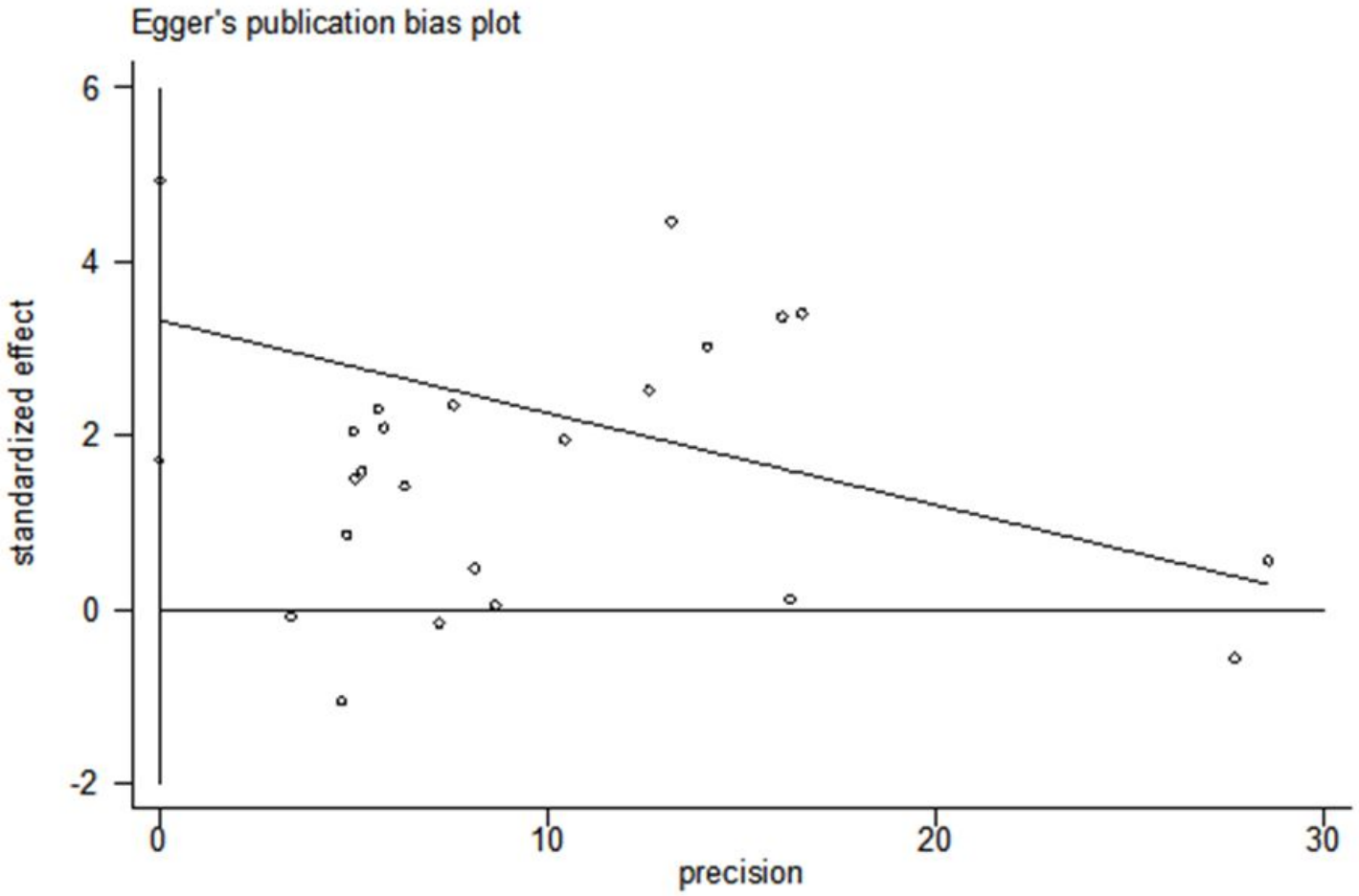

Figure 4

Egger's linear regression.