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Original Article

Meta-analysis on the association between PADI4 polymorphisms and rheumatoid arthritis in a Chinese population

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Abstract: Background: Although various individual studies have evaluated the correlation between peptidylarginine deiminase 4 (PADI4) polymorphisms and rheumatoid arthritis (RA), the results remain inconclusive. Therefore, here a meta-analysis in the Chinese population was performed to provide comprehensive data on an association between PADI4 polymorphism and RA. Methods: Studies were identified using PubMed and Chinese databases through May 2018. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strengths of these associations. Results: This meta-analysis included 14 studies with 2188 RA cases and 2490 controls. Significant association of PADI4_94, PADI4_104, and PADI4_92 polymorphisms and RA was observed in the Chinese population. Pooled estimates for the other polymorphisms were not statistically significantly associated with RA (PADI4_89, _90). Conclusions: This meta-analysis provides evidence that PADI4_94, PADI4_104, and PADI4_92 variants might be risk alleles for RA susceptibility in Chinese individuals. Further studies conducted in other ethnic groups are required for definitive conclusions.

Keywords: Meta-analysis, peptidylarginine deiminase 4, polymorphism, rheumatoid arthritis, Chinese

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease predominantly affecting the synovial joints and suffered by up to 1% of adults worldwide [1-3]. The inflammatory cytokines and an imbalance between pro- and anti-inflammatory cytokine factors may induce and aggravate the immunoreaction, chronic inflammation, and tissue destruction in RA joints [4-6], however molecular mechanisms relating to RA are still being investigated and genetic polymorphisms are gaining increasing attention [7]. In recent years, many candidate genes have been identified as potential RA susceptibility loci. Of these genes, an important one is peptidylarginine deiminase 4 (PADI4), which is mainly distributed in the cells of various hematopoietic lineages, and expressed at high levels in the inflamed synovium of patients with RA. The PADI4 gene is on chromosome 1p36, and several polymorphisms have been identified in its promoter. The PADI4_94, _104, _92, _89, and _90 polymorphisms have been the most extensively examined in studies on PADI4 polymorphisms in RA.

Several previous studies have explored an association between the PADI4 polymorphisms and RA susceptibility, however the results are inconsistent. Differences in findings may be due to race and clinical heterogeneity in patients who have been studied, as well as a limited number of patients in each study. Meta-analysis is one way to overcome the problems of small sample size and inadequate statistical power. In order to lessen the influence of differing genetic backgrounds, a meta-analysis was performed to assess the relationship between PADI4_94, _104, _92, _90, and _89 polymorphisms and the risk for RA in the Chinese population.

Materials and methods

Search strategy and selection criteria

A search was performed for studies that examined associations between PADI4 polymor-

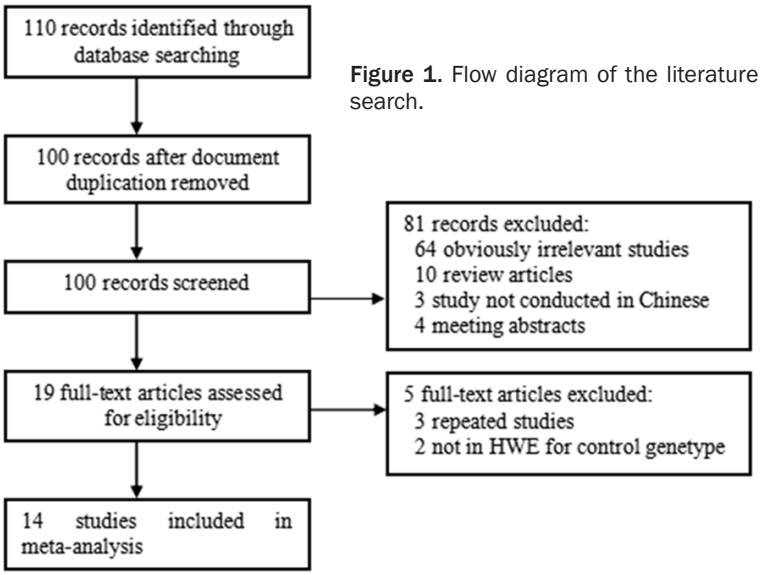

Figure 1. Flow diagram of the literature search.

phisms and RA before May 2018. The literature was searched using the PubMed and Chinese databases to identify available articles in which PADI4 polymorphisms were analyzed in RA patients. The search keywords were used: (PADI4 or peptidylarginine deiminase 4) and (rheumatoid arthritis or RA) and (Chinese or China or Taiwan). References in identified studies were also investigated to identify additional studies not indexed by the electronic databases. No language restriction was applied.

Inclusion criteria: (1) case-control or cohort studies describing the association of the PADI4 polymorphisms and RA, (2) provided the genotypes in cases and controls, (3) all patients were diagnosed according to the classification criteria proposed by the American College of Rheumatology for RA in 1987, (4) participants were Chinese population, (5) genotypes distribution in control groups was in the Hardy-Weinberg equilibrium (HWE). Exclusion criteria: (1) repeated literatures, (2) incomplete data, (3) case-only articles, (4) review articles and abstracts.

Data extraction

A systematic review and meta-analysis was conducted in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Data were extracted from all eligible publications by two independent reviewers. Any discrepancy between the reviewers was resolved by a discussion between the two reviewers. Titles and abstracts of all identified studies were screened first. Full articles were scrutinized if the title and abstract were ambiguous. The following information was collected from each study: first author's name, publication year, source of controls, sample size, and available genotype information from the PADI4 polymorphisms. Hardy-Weinberg equilibrium in controls were calculated from corresponding genotype distributions. Source of controls was stratified to population based [PB] and hospital based [HB].

Statistical analysis

Meta-analyses was performed using: (1) allelic contrast, (2) contrast of homozygotes, (3) recessive, and (4) dominant models. Allele frequencies at the PADI4 polymorphisms from the respective studies were determined by the allele counting method. The pooled odds ratio (ORs) and corresponding 95% confidence intervals (CIs) were calculated to assess the relationship between PADI4 polymorphisms and RA risk. The between-study heterogeneity was assessed by Chi-square based Q-test [8]. Depending on the results of the heterogeneity test among individual studies, the fixed-effect model (Mantel-Haenszel) or random-effect model (DerSimonian and Laird) was selected to summarize the combined ORs and their 95% CIs. The significance of the pooled OR was determined by a Z-test. Sensitivity analysis was evaluated by comparing the results of fixed-effects model and random-effects model. 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 in the form of a flow chart. A total of 100 articles that examined the association between PADI4 polymorphisms and risk of RA were identified after document duplication removed in

Table 1. Characteristics of studies included in the meta-analysis

References	Publication year	Source of controls	Case number	Control number	Studied polymorphisms
Cui et al. [14]	2007	PB	92	116	PADI4_94, _104
Lu et al. [15]	2007	PB	41	56	PADI4_89, _90, _92, _104
Feng et al. [16]	2009	PB	115	106	PADI4_94
Wen et al. [17]	2009	PB	105	96	PADI4_92
Shi et al. [18]	2010	PB	112	97	PADI4_94, _104
Feng et al. [19]	2010	PB	115	106	PADI4_104
Zhong et al. [20]	2010	PB	302	322	PADI4_92
Chen et al. [21]	2011	PB	378	204	PADI4_89, _90, _94, _104
Cui et al. [22]	2011	PB	134	140	PADI4_94
Xu et al. [23]	2011	PB	130	130	PADI4_94, _104
Cheng et al. [24]	2012	HB	329	697	PADI4_92, _94
Li et al. [25]	2012	HB	53	42	PADI4_92, _104
Liu et al. [26]	2012	PB	90	90	PADI4_94, _104
Li et al. [27]	2013	PB	192	288	PADI4_94

different databases. After screening the titles and abstracts, 81 articles were excluded because they were review articles, meeting abstracts, not Chinese population, or irrelevant to the current study. Of the 19 potentially relevant articles [9-27] identified for full study retrieval, three [9-11] were excluded due to repeated studies, two [12-13] were excluded because of deviations from the HWE in control groups. Finally, 14 case-control studies [14-27] met the inclusion criteria. The publication year of involved studies ranged from 2007 to 2013. In total, 2188 RA cases and 2490 controls were included in this meta-analysis. The source of controls in 12 studies was population-based. There were 9 studies on _94G/A, 8 studies on _104C/T, 5 studies on _92C/G, 2 studies on _89A/G, and 2 studies on _90C/T. Characteristics of included studies are summarized in **Table 1**.

Meta-analysis

The summary of the meta-analysis on the association between PADI4 gene polymorphisms and RA in the Chinese population is shown in **Table 2**.

PADI4_94G/A polymorphism and RA

Nine studies determined the relationship between the PADI4_94G/A polymorphism and RA risk in the Chinese population [14, 16, 18, 21-24, 26, 27]. The total sample size for patients with RA and controls was 1572 and 1868, respectively. Meta-analysis revealed that the PADI4_94G/A variants were significantly associated with an increased risk of RA in three models (A vs. G: OR=1.25, 95% CI=1.13-1.38, **Figure 2**; AA vs. GG: OR=1.52, 95% CI=1.24-1.85; AA+GA vs. GG: OR=1.54, 95% CI=1.22-1.95).

PADI4_104C/T polymorphism and RA

Eight studies including 1011 cases and 841 controls identified an association between the PADI4_104C/T polymorphism and RA risk in the Chinese population [14, 15, 18, 19, 21, 23, 25, 26]. A significant association was observed in two models (T vs. C: OR=1.44, 95% CI=1.11-1.87, **Figure 3**; TT+CT vs. CC: OR=1.78, 95% CI=1.19-2.65).

PADI4_92C/G polymorphism and RA

Five studies containing 830 cases and 1213 controls examined the association of PADI4_92C/G and RA in the Chinese population [15, 17, 20, 24, 25]. Results indicated a significant association between the PADI4_92C/G polymorphism and RA in all models (G vs. C: OR=1.62, 95% CI=1.16-2.26, **Figure 4**; GG vs. CC: OR=1.63, 95% CI=1.25-2.14; GG vs. CC+CG: OR=1.47, 95% CI=1.16-1.86; GG+CG vs. CC: OR=2.22, 95% CI=1.21-4.10).

PADI4_89A/G, PADI4_90C/T polymorphism and RA

Only two studies containing 419 cases and 260 controls examined the association of PADI4_89A/G, PADI4_90C/T and RA in the Chi-

Table 2. Association of the PADI4 gene polymorphisms on RA susceptibility

Polymorphism		n	ORr (95% CI)	ORf (95% CI)	P_h
PADI4_94G/A	A vs. G	9	1.25 (1.12-1.40)	1.25 (1.13-1.38)	0.286
	AA vs. GG	9	1.52 (1.24-1.87)	1.52 (1.24-1.85)	0.404
	AA vs. GG+GA	9	1.19 (1.00-1.41)	1.19 (1.00-1.41)	0.864
	AA+GA vs. GG	9	1.54 (1.22-1.95)	1.47 (1.26-1.71)	0.026
PADI4_104C/T	T vs. C	8	1.44 (1.11-1.87)	1.29 (1.13-1.48)	0.001
	TT vs. CC	7	1.45 (0.99-2.13)	1.38 (1.04-1.83)	0.144
	TT vs. CC+CT	7	1.19 (0.86-1.64)	1.17 (0.90-1.52)	0.232
	TT+CT vs. CC	8	1.78 (1.19-2.65)	1.53 (1.26-1.85)	0.000
PADI4_92C/G	G vs. C	5	1.62 (1.16-2.26)	1.35 (1.19-1.54)	0.001
	GG vs. CC	4	1.63 (1.25-2.14)	1.63 (1.25-2.14)	0.575
	GG vs. CC+CG	5	1.47 (1.16-1.86)	1.47 (1.16-1.86)	0.935
	GG+CG vs. CC	5	2.22 (1.21-4.10)	1.50 (1.24-1.82)	0.000
PADI4_89A/G	G vs. A	1	-	-	-
	GG vs. AA	1	-	-	-
	GG vs. AA+AG	1	-	-	-
	GG+AG vs. AA	2	1.52 (0.70-3.28)	1.27 (0.91-1.76)	0.081
PADI4_90C/T	T vs. C	1	-	-	-
	TT vs. CC	1	-	-	-
	TT vs. CC+CT	1	-	-	-
	TT+CT vs. CC	2	3.51 (0.35-35.25)	1.57 (1.13-2.17)	0.000

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

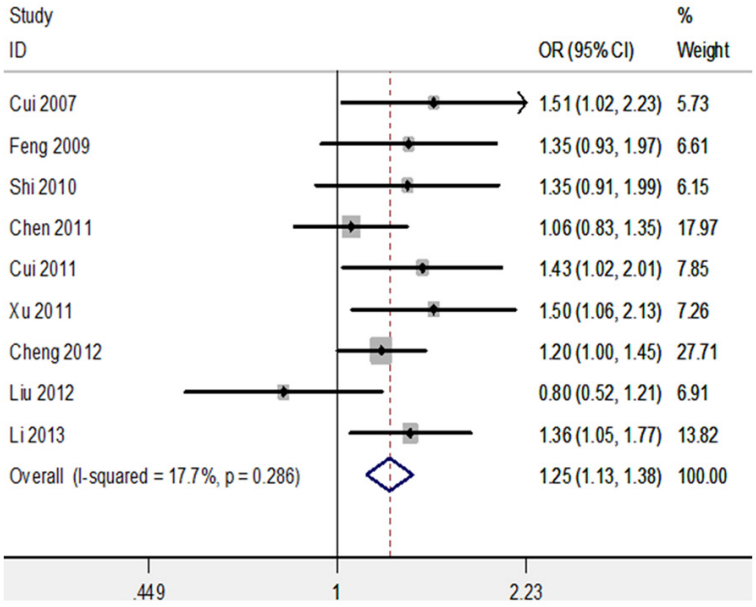

Figure 2. Forest plots on the association between PADI4_94G/A polymorphism and RA risk in Chinese (for allele model A vs. G).

nese population [15, 21]. No association was detected between PADI4_89A/G, PADI4_90C/T and RA.

Sensitive analysis

To validate the credibility of the outcomes of this meta-analysis, a sensitivity analysis was performed by comparing results of random-effects and fixed-effects models. All the significant results were not materially altered except the association between PADI4_104C/T and RA in homozygotes model (**Table 2**), indicating that the results were relatively stable and credible.

Discussion

Convincing evidence has emerged that individual susceptibility to RA is partially determined by a number of genetic variations. The relationship between PADI4 polymorphisms and RA risk has attracted the attention of both doctors and researchers. Since the first positive association

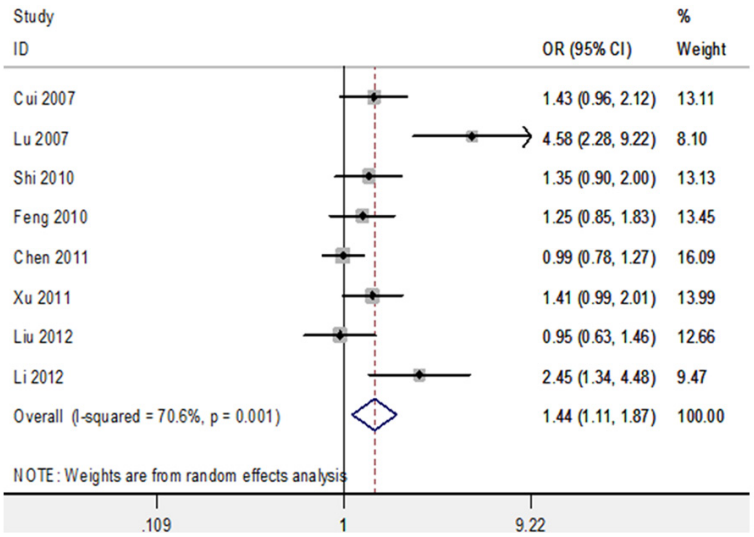

Figure 3. Forest plots on the association between PADI4_104C/T polymorphism and RA risk in Chinese (for allele model T vs. C).

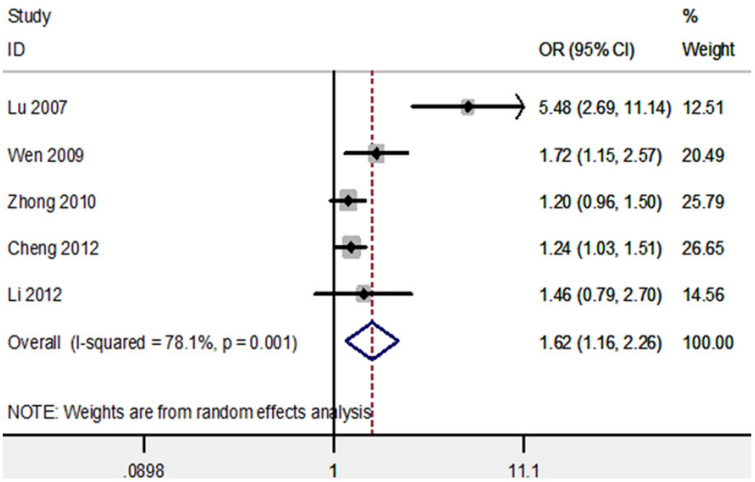

Figure 4. Forest plots on the association between PADI4_92C/G polymorphism and RA risk in Chinese (for allele model G vs. C).

between PADI4 and RA was reported in a Japanese population [28], a number of studies have reported the association between PADI4 polymorphisms and RA risk, but the results have been inconclusive. Regional and racial differences are likely reasons for the conflicting results. Therefore, a meta-analysis was completed to assess the effect of the PADI4 polymorphisms on risk for RA in the Chinese population specifically, in order to reduce the impact of genetic background. A total of 14 studies with 2188 RA cases and 2490 controls were included in this meta-analysis. The studies were combined to evaluate genetic associations between RA and the most commonly studied polymorphisms, PADI4_94, _104, _92, _89, and _90. A significant association of the PADI4_94, PADI4_104, and PADI4_92 polymorphisms with susceptibility to RA was found in the Chinese population. No association was found between PADI4_89 or PADI4_90 and RA in Chinese individuals.

Currently, there are several published meta-analyses regarding PADI4 polymorphisms and RA risk [29-33]. Of these, two meta-analyses [29, 31] found that the PADI4-92C/G polymorphism had a positive association with RA in Asians, but not in Caucasians, while Yang et al. [30] found a significant result only in Africans; one meta-analysis reported that there was significant association between PADI4-104C/T polymorphism and RA risk both in Asian and European population [29], while two meta-analyses reported significant association only in Asian individuals [31, 32]; one meta-analysis reported significant association between PADI4-94G/A polymorphism and RA risk both in Asian and European population [33], while two reported no significant association in European population [30, 31]. However, no one meta-analysis was conducted in a separate ethnic group. In comparison, these previously published meta-analyses only included a smaller number of studies which were conducted in Chinese populations, and did not calculate pooled ORs for all studies in Chinese populations. This current meta-analysis is strengthened by investigating the association only in a Chinese ethnicity, which revealed significant results in Chinese individuals. The association between PADI4 polymorphisms

and RA was able to be explored and may not be influenced by genetic backgrounds and living environment.

With regard to the association between PADI4_89 or PADI4_90 and RA, inconsistent results were also found in these meta-analyses [29-32]. An association of the PADI4_89 or PADI4_90 polymorphisms with RA susceptibility in Chinese people was not supported, and we did not find an association between these PADI4 polymorphisms and RA susceptibility in Chinese individuals in the meta-analysis under a dominant model. However, our results should be interpreted with caution because of the limited number of studies on PADI4_89 or PADI4_90 polymorphisms. The relative importance of the PADI4 gene polymorphism in the development of RA may be different between ethnic groups. However, we were unable to perform meta-analyses of the PADI4_89 and PADI4_90 polymorphisms in other ethnicity due to this ethnic-specific data.

Several limitations of this study are to be noted. First, this ethnic-specific meta-analysis only included data from Chinese patients, and thus, our results are only applicable to this ethnic group. Second, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Third, the etiology of RA is complex and is mediated by the activities of multiple genes. The effect of any single gene might have a limited impact on RA risk than have been anticipated so far. Finally, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis.

In conclusion, the results of this meta-analysis suggest that the PADI4_94, PADI4_104, and PADI4_92 polymorphisms are associated with susceptibility to RA in the Chinese population. Ethnicity seems to play an important role in the genetic association of the disease. Further studies in other ethic groups are required in order to explore the broader role that these polymorphisms play in the pathogenesis of RA.

Disclosure of conflict of interest

None.

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