

# Are programmed cell death 1 gene polymorphisms correlated with susceptibility to rheumatoid arthritis?

## A meta-analysis

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### Abstract

**Background:** Several studies investigated the relationship between programmed cell death 1 (*PDCD1*) gene polymorphisms and rheumatoid arthritis (RA) risk, but the results were controversial. To explore whether *PDCD1* gene polymorphisms have an effect on RA risk, we conducted this meta-analysis to investigate the relationships between *PDCD1* polymorphisms (rs36084323 [PD-1.1 G/A], rs11568821 [PD-1.3 G/A] and rs2227981 [PD-1.5 C/T]) and RA risk under 4 genetic models.

**Methods:** PubMed, EMBASE, Web of Science, Cochrane Library China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBLM) were systematically searched for all eligible case-control studies. The last search was updated on September 10, 2016. Studies were accessed using Newcastle-Ottawa Scale case control study (NOS), and the combined effect size was calculated using STATA software, version 12.0. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to assess the association. Heterogeneity analysis and subgroup analysis were also performed. Sensitivity analysis and publication bias were also performed if necessary.

**Results:** This meta-analysis included 6 studies. The result demonstrated null association between rs36084323 (PD-1.1 G/A) polymorphism and RA susceptibility in all 4 genetic models. With regard to rs11568821 (PD-1.3 G/A), statistically significant association with RA risk was observed under allele model in Caucasians (allele model A vs G, OR = 1.19, 95% CI = 1.03–1.41). There was no significant association between rs2227981 (PD-1.5 C/T) polymorphism and RA risk.

**Conclusion:** The present study suggests that mutant A allele in rs11568821 (PD-1.3 G/A) might increase the susceptibility to RA in Caucasians.

**Abbreviations:** AS = ankylosing spondylitis, CBLM = Chinese Biomedical Literature Database, CI = confidence interval, CNKI = Cochrane Library China National Knowledge Infrastructure, HWE = Hardy-Weinberg equilibrium, NOS = Newcastle-Ottawa Scale case control study, OR = odds ratio, *PDCD1* = programmed cell death 1, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus, T1DM = type I diabetes mellitus.

**Keywords:** meta-analysis, programmed cell death 1, rheumatoid arthritis

## 1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory, autoimmune disease characterized by joint inflammation and synovitis, which could lead to cartilage and bone destruction, disability,

and eventually, to systemic complications including cardiovascular and pulmonary disorders.<sup>[1]</sup> Interactions between genetic susceptibility and environmental factors have been found to play an important role in the pathogenesis and progression of RA.<sup>[2]</sup> Genetic risks for RA have been acknowledged for years, various new genetic risk factors for RA were identified with the help of genome-wide association studies (GWAS), such as HLA-DRB1, PADI4, PTPN22, TNFAIP3, STAT4, AFF3, and CCR6.<sup>[3–6]</sup> Despite these risk factors, the contribution of these individual risk loci to the development of RA appears to be variable,<sup>[7]</sup> the exact pathogenesis of RA still needs to be elucidated.

Programmed cell death 1 (*PDCD1* or PD1), whose gene is localized on chromosome 2q37.3, is a member of the CD28/B7 family receptors, encoding a 55 kDa immunosuppressive receptor in T cells, B cells, and myeloid cells.<sup>[8]</sup> *PDCD1* is a necessary negative regulator of autoimmunity regulation; the interactions between *PDCD1* and its ligands, PD-L1 and PD-L2, have a negative effect in T cell receptor-mediated lymphocyte proliferation and cytokine secretion, and could inhibit CD28-mediated costimulation.<sup>[9]</sup> It also regulated the induction and maintenance of T cell tolerance, which could protect tissues from effector T cell responses-mediated tissue damage.<sup>[8,10,11]</sup> For

Editor: Ilke Coskun Benlidayi.

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The authors declare that they have no conflicts of interest.

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Medicine (2017) 96:35(e7805)

Received: 13 September 2016 / Received in final form: 21 July 2017 / Accepted: 26 July 2017

<http://dx.doi.org/10.1097/MD.0000000000007805>

instance, a recent study indicated that *PDCD1* upregulated on regulatory T cells enhances the suppression of CD8+ T cell immune response via the interaction with PD-L1 expressed on CD8+ T cells,<sup>[12]</sup> and another study showed that genetic absence of *PDCD1* promoted accumulation of terminally differentiated CD8+ T cells.<sup>[13]</sup> The lack of *PDCD1* could result in the development of autoimmune diseases, such as systemic lupus erythematosus (SLE),<sup>[14]</sup> type I diabetes mellitus (T1DM),<sup>[15]</sup> and ankylosing spondylitis (AS).<sup>[13]</sup>

RA is a chronic autoimmune and inflammatory disorder, featured by immune-mediated inflammatory circumstances of the synovium. In RA synovial fluid, the PD-1<sup>+</sup> T cells are enriched and consist of a unique allergic T cell subset in synovial fluid of RA patients.<sup>[16]</sup> The *PDCD1* gene has several polymorphisms, including rs36084323 (PD-1.1 G/A), rs11568821 (PD-1.3 G/A), rs2227981 (PD-1.5 C/T), and rs2227982 (PD-1.9 C/T), which could influence the biological function of *PDCD1*. *PDCD1* gene polymorphisms were found to be correlated with the risk of several autoimmune diseases, such as SLE, RA, diabetes mellitus, and multiple sclerosis (MS).<sup>[17]</sup> Several studies aimed to investigate the relationship between *PDCD1* gene polymorphisms and RA risk, but the results were controversial.<sup>[18–23]</sup> For instance, Prokunina et al confirmed there is an association between rs11568821 (PD-1.3 G/A) polymorphism and the risk of RA in the Caucasian population, which was supported by the study of Tahoori et al.<sup>[20]</sup> However, Iwamoto et al<sup>[21]</sup> and Liu et al<sup>[19]</sup> hold a different opinion. In order to provide a comprehensive assessment of the association between the polymorphisms of *PDCD1* and RA risk, we conducted this meta-analysis.

## 2. Material and methods

No ethical approval and informed consent are necessary for this meta-analysis, and it was reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.<sup>[24]</sup>

### 2.1. Literature research

We systematically searched databases including PubMed, EMBASE, Web of Science, Cochrane Library China National Knowledge Infrastructure (CNKI), and Chinese Biomedical Literature Database (CBLM) for all eligible case-control studies with a retrieval strategy. The last search was updated on September 10, 2016. The following search terms were used: rheumatoid arthritis OR RA and programmed cell death 1 OR *PDCD1* OR PD-1 OR PD-1.1 OR rs36084323 OR PD-1.3 OR rs11568821 OR PD-1.5 OR rs2227981 OR PD-1.9 OR rs2227982, and polymorphism OR polymorphisms OR single nucleotide polymorphism OR SNP OR variation. Publication language was not restricted in our study selection. Additional eligible studies were identified by searching the references of all the selected articles.

### 2.2. Inclusion criteria and publication quality assessment

Inclusion criteria of this meta-analysis were as follows: case-control studies; investigation of the relationship between RA risk with at least 1 of *PDCD1* gene polymorphisms, including rs36084323 (PD-1.1 G/A), rs11568821 (PD-1.3 G/A), rs2227981 (PD-1.5 C/T), and rs2227982 (PD-1.9 C/T); and enough data were provided for analysis. Newcastle-Ottawa Scale was used to assess the quality of all the eligible studies in the following 3 aspects: selection, comparability, and exposure. Scores ranging from 0 to 9 were used to evaluate

the quality of the original studies. A score of 6 or above was considered as high quality.

### 2.3. Data extraction

All the eligible studies were independently reviewed by 2 authors. Any disagreement about data was settled through a team discussion until a consensus was reached. For each study, the following data were collected: author list, year of publication, ethnicity, genotyping method, genotypes frequency in each polymorphism, diagnostic criteria, matching criteria, source of RA, source of control, and NOS scores.

### 2.4. Statistical analysis

We performed a meta-analysis to assess the association between *PDCD1* polymorphisms and RA susceptibility. Chi-square test was used to evaluate whether the genotype distributions of each control group followed the Hardy-Weinberg equilibrium (HWE), significant  $P < .05$  was considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association between *PDCD1* polymorphisms and RA risk in 4 genetic models which were dominant, recessive, codominant, and additive. Subgroup analysis was performed based on ethnicity (Asians or Caucasians). The chi-squared-based  $Q$  statistical test and  $I^2$  metric value were used to assess the statistical heterogeneity between studies. If the  $I^2$  value is  $>50\%$  or  $P_Q < .10$ , a difference in statistical heterogeneity existed, ORs were pooled by the random-effect model, otherwise, the fixed-effect model was applied.<sup>[25]</sup> Publication bias was examined by a funnel plot and Egger test. If the  $P$  value in Egger test was less than .05, publication bias was statistically significant. Otherwise, the study was considered to have no publication bias.

All statistical analyses were performed using Stata 12.0 software (StataCorp, College Station, TX) and all  $P$  values were considered 2-sided, unless otherwise stated.

## 3. Results

### 3.1. Study characteristics

A total of 6 studies<sup>[18–23]</sup> investigated the relationship of *PDCD1* polymorphisms and RA risk fulfilled the eligibility criteria. The study selection process is shown in Figure 1. There were 4 studies involving 2094 cases and 1591 controls that reported the relationship between rs36084323 (PD-1.1 G/A) polymorphism and RA.<sup>[19–22]</sup> Three studies involving 1382 cases and 3720 controls focused on the relationship between rs11568821 (PD-1.3 G/A) polymorphism and RA.<sup>[18–21,23]</sup> Another 3 studies including 1985 RA cases and 1400 controls studied the relationship between rs2227981 (PD-1.5 C/T) polymorphism and RA.<sup>[19,21,22]</sup> Moreover, rs11568821 (PD-1.3 G/A) was nonpolymorphic in Asians and so was rs2227981 (PD-1.5 C/T) in Caucasians. Because there were only 2 studies exploring rs2227982 (PD-1.9 C/T) polymorphism, we excluded it in our study. The general demographics characters of all these studies are shown in Table 1. The genotype distribution in the control subjects in all studies was consistent with HWE.

### 3.2. Meta-analysis results

**3.2.1. rs36084323 (PD-1.1 G/A) polymorphism and RA susceptibility in Caucasians or in Asians.** For the association between rs36084323 (PD-1.1 G/A) and the risk of RA, 4 studies

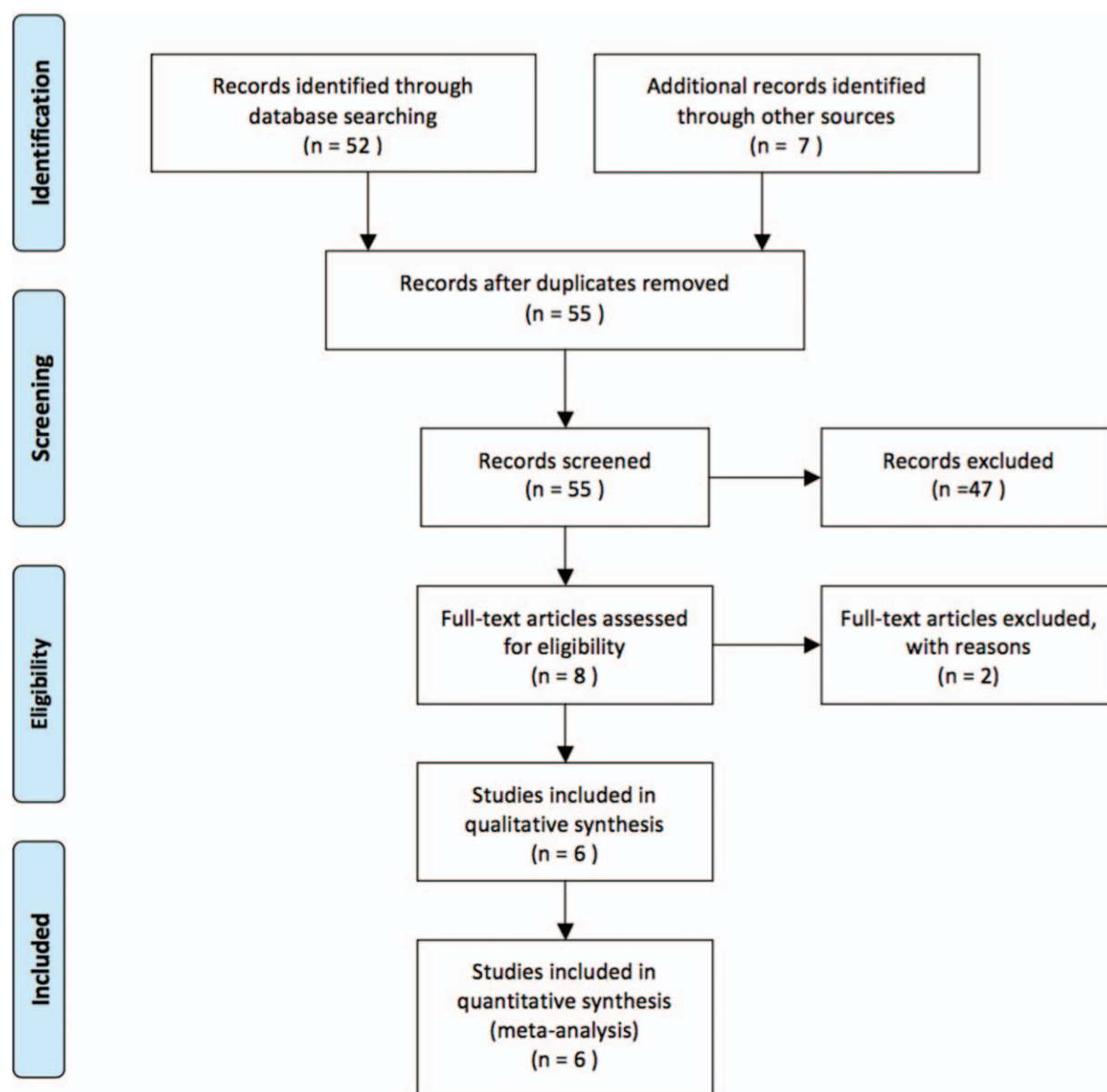


Figure 1. The study selection and inclusion process.

were included according to the match criteria. Significant heterogeneity existed in all genetic models, so we applied random-effect model. We found null association between rs36084323 (PD-1.1G/A) and RA risk in any of the 4 genetic models based on random-effect model. Because there was only 1 study in Caucasian population, we conduct ethnicity subgroup analysis in Asians. Similarly, we failed to find any association in any of the 4 genetic models based on random-effect model. All the results are shown in Table 2. The forest plot for the additive model based on the random-effect model was selected to perform the pooled OR as shown in Figure 2.

**3.2.2. rs11568821 (PD-1.3G/A) polymorphism and RA susceptibility in Caucasians or in Asians.** As for rs11568821 (PD 1.3G/A), 3 studies were included. We applied fixed-effect model because there was no significant heterogeneity in any of the 4 genetic models. There was no rs11568821 (PD-1.3G/A) polymorphism in Asian populations, we only conducted analysis

in Caucasian. We observed significant correlation between rs11568821 (PD-1.3G/A) and RA risk in additive model and dominant model (A vs G: OR=1.20, 95% CI=1.03–1.41; AG + AA vs GG: OR=1.19, 95% CI=1.01–1.41) in Caucasian. Table 2 showed the results of statistical analyses. The forest plot for the additive model is given in Figure 3.

**3.2.3. rs2227981 (PD-1.5C/T) polymorphism and RA susceptibility in Asians.** With regard to rs2227981 (PD-1.5C/T), our study included 3 studies, which were conducted in Asian population. The results indicated that there was no significant association between rs2227981 (PD-1.5C/T) polymorphisms and RA risk in any of 4 genetic models. All the results were listed in Table 2. The forest plot for the additive model is given in Figure 4.

**3.2.4. Publication bias.** Publication bias was assessed by Begg funnel plots and Egger test. Significant publication bias was not observed in any meta-analysis of the 3 polymorphisms under

**Table 1**

**General characteristics of the eligible studies.**

Author	Year	Ethnicity	Genotyping methods	rs36084323 (PD-1.1 G/A)						rs11568821 (PD-1.3 G/A)						rs2227981 (PD-1.5 C/T)						Matching criteria	Source of RA	Source of control	NOS score
				Case			Control			Case			Control			Case			Control						
				GG	AG	AA	GG	AG	AA	GG	AG	AA	GG	AG	AA	GG	AG	AA	GG	AG	AA				
Prokunia et al	2004	Caucasian	PCR-RFLP	-	-	-	985	180	10	2927	458	19	89	69	22	333	259	55	ACR revised criteria	Sex and age	S	PB and HB	8		
Kong et al	2005	Asian	TaqMan	63	92	25	177	309	161				714	615	156	217	178	49	ACR revised criteria	NA	S	PB	7		
Iwamoto et al	2007	Asian	TaqMan	360	722	392	124	203	120										ACR	Sex and age	S	NA	6		
Tahoori et al	2011	Caucasian	PCR-RFLP	114	5	1	185	3	0	93	26	1	151	36	1				ACR	NA	S	PB	7		
Liu et al	2014	Asian	Direct sequencing	97	144	79	69	144	96				175	118	27	145	130	34	ACR	Sex and age	S	HB	8		
Canto et al	2015	Caucasian	PCR-RFLP				71	12	4	110	16	2							ACR	NA	S	PB	7		

ACR=American College of Rheumatology, HB=hospital base, NA=not available, NOS = Newcastle-Ottawa Scale case control study, PB = population base, RA = rheumatoid arthritis, RFLP = restriction-fragment length polymorphism, S/F =sporadic/familial.

addictive model ( $t=0.18, P=.87$  for rs36084323 [PD-1.1 G/A];  $t=0.97, P=.51$  for rs11568821 [PD-1.3 G/A];  $t=-0.18, P=.89$  for rs2227981 [PD-1.5 C/T]). The shape of the Begg funnel plots in the overall population did not reveal any obvious asymmetry.

**4. Discussion**

RA is one of the most common and the typical representative of autoimmune diseases, characterized by synovial tissue inflammation and progressive destruction cartilage, which is one of the strongest predictors of long-term outcome and disability in RA patients.<sup>[26,27]</sup> Environmental and genetic factors participate in the pathogenesis of RA.<sup>[28,29]</sup> Recently, studies have focused on the identification of genes that influenced the susceptibility to this disease, among them was *PDCD1*, which was an important negative regulator of autoimmunity. This gene not only plays an important role in the regulation of the induction and maintenance of T cell tolerance, but also inhibits effector T cell responses and protects tissues from autoimmune-mediated tissue damage.<sup>[8,10,11]</sup> Therefore, it is considered to be a strong candidate gene responsible for autoimmune diseases, especially for RA.<sup>[22]</sup> As indicated, *PDCD1* gene polymorphisms are associated with autoimmune disorders, such as SLE,<sup>[29]</sup> T1D,<sup>[30]</sup> and AS<sup>[31]</sup> (one of our previous studies).

Though a number of studies have investigated the association between *PDCD1* polymorphism and susceptibility to RA, the results remain controversial. In this meta-analysis, we quantitatively evaluated the correlation between 3 SNPs of *PDCD1* gene and RA susceptibility.

The rs36084323 (PD-1.1 G/A) is located in the promoter of *PDCD1* gene (Gene Bank accession no. AF363458). Transcription initiation is an important part of regulation in gene expression. Polymorphisms that occurred in the promoter could affect the normal process of gene activation and transcriptional initiation, thus increase or decrease the quantity of mRNA and protein.<sup>[32]</sup> Theoretically, PD-1.1 should be the most likely polymorphism site associated with RA risk. However, we failed to detect significant association of rs36084323 (PD-1.1 G/A) polymorphism and RA risk according to our results. When further stratified by ethnicity, our results indicated null association in Asian populations. The limited studies and generally small sample size may affect the accuracy of this result especially given that only 1 study was conducted in Caucasian populations.

For rs11568821 (PD-1.3 G/A) polymorphism, statistical significance was observed between rs11568821 (PD-1.3 G/A) polymorphism and risk of RA. This result was consistent with a previous meta-analysis by Lee et al.<sup>[30]</sup> Considering only 2 studies were involved in their study, our result improved the credibility of the conclusion. Even so, extra cautious should be taken because of the generally limited number of studies and the OR value, which was close to 1. The rs11568821 (PD-1.3 G/A) is located in intron 4, in general, polymorphic sequence variations are considered to be rather harmless, especially if located in noncoding parts of a gene. It may be that the Rs11568821 (PD-1.3 G/A) is not itself the responsible allele, but is in linkage disequilibrium with the true causative allele. Although rs11568821 (PD 1.3 G/A) polymorphism has been found to be significantly associated with the risk of developing RA, the interactive function of *PDCD1* SNPs and other genes may have an important role in the etiology and development of RA.<sup>[22]</sup>

Similar to rs36084323 (PD-1.1 G/A), there was null significant association between rs2227981 (PD-1.5 C/T) and susceptibility

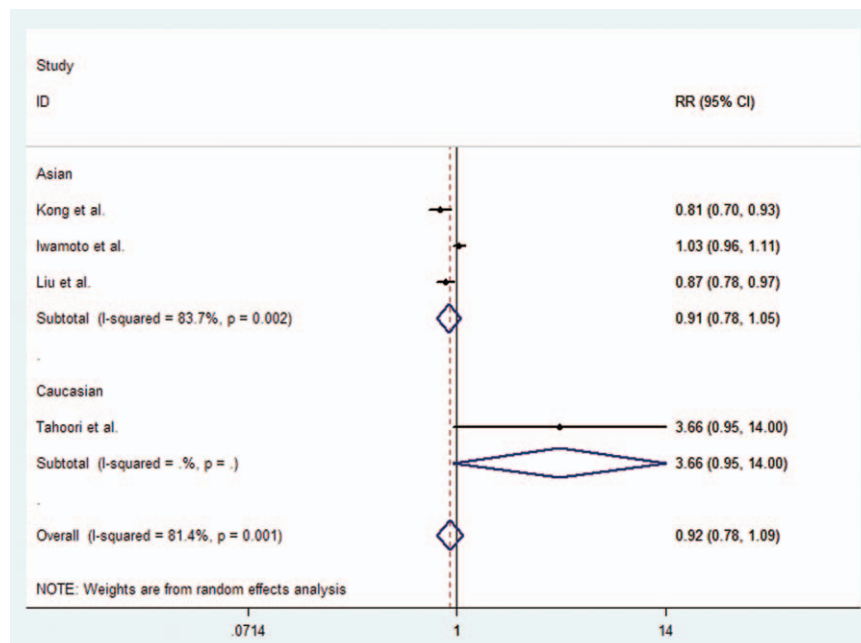
**Table 2**  
**Results of genetic models for rs36084323 (PD-1.1 G/A), rs11568821 (PD-1.3 G/A), and rs2227981 (PD-1.5 C/T) polymorphisms and RA.**

Polymorphism sites	Genetic model	Ethnicity	No. of studies	Test for association			Test for heterogeneity			Test mode
				OR (95% CI)	Z	P	χ <sup>2</sup>	P	I <sup>2</sup> , %	
rs36084323 (PD-1.1 G/A)	A vs G	Asian	3	0.91 (0.78–1.06)	1.29	.20	12.4	.002	83.7	R
		Caucasian	1	3.66 (0.96–14.00)	1.57	.12	0.0	.00	0.00	F
		Overall	4	0.92 (0.78–1.10)	0.88	.38	15.41	.002	81.4	R
	AG + AA vs GG	Asian	3	0.83 (0.56–1.25)	0.88	.38	10.00	.007	80.0	R
		Caucasian	1	2.57 (0.63–10.45)	0.32	.19	0.0	.00	0.00	F
		Overall	4	0.90 (0.60–1.35)	0.51	.61	12.06	.007	75.1	R
	AA vs AG + GG	Asian	3	0.73 (0.50–1.08)	1.57	.12	7.75	.02	74.2	R
		Caucasian	1	3.78 (0.15–93.52)	0.57	.12	0.0	.00	0.00	F
		Overall	4	0.75 (0.51–1.10)	1.48	.14	8.62	.04	65.2	R
	AG vs GG	Asian	3	0.92 (0.66–1.30)	0.46	.64	6.26	.04	68.1	R
		Caucasian	1	2.14 (0.50–9.11)	1.03	.30	0.0	.00	0.00	F
		Overall	4	0.96 (0.69–1.34)	0.24	.81	7.35	.06	59.2	R
AA vs GG	Asian	3	0.68 (0.38–1.22)	1.29	.20	12.83	.002	84.4	R	
	Caucasian	1	3.85 (0.16–95.2)	0.82	.41	0.0	.00	0.00	F	
	Overall	4	0.72 (0.40–1.27)	1.14	.25	13.74	.003	78.2	R	
rs11568821 (PD-1.3 G/A)	A vs G	Caucasian	3	1.18 (1.02–1.37)	2.28	.02	0.56	.76	0.00	F
	AG + AA vs GG	Caucasian	3	1.19 (1.01–1.41)	2.05	.04	0.15	.93	0.00	F
	AA vs AG + GG	Caucasian	3	1.73 (0.88–3.38)	1.60	.11	0.51	.77	0.00	F
	AG vs GG	Caucasian	3	1.17 (0.98–1.39)	1.76	.08	0.00	1.00	0.00	F
	AA vs GG	Caucasian	3	1.74 (0.88–3.45)	1.60	.11	0.51	.78	0.00	F
rs2227981 (PD-1.5 C/T)	C vs T	Asian	3	0.98 (0.85–1.12)	0.33	.75	5.01	.08	60.1	R
	TC + TT vs CC	Asian	3	0.96 (0.82–1.12)	0.52	.60	3.83	.15	47.7	F
	TT vs TC + CC	Asian	3	0.99 (0.77–1.28)	0.08	.93	3.56	.17	43.9	F
	TC vs CC	Asian	3	0.96 (0.53–1.13)	0.53	.59	2.72	.26	26.4	F
	TT vs CC	Asian	3	0.98 (0.66–1.47)	0.08	.93	4.32	.12	53.7	R

RA = rheumatoid arthritis.

to RA under 4 genetic models. All 3 studies involved in the relationship between rs2227981 (PD-1.5 C/T) polymorphism and RA risk were from Asian populations. In order to further verify this result, studies from other populations should be addressed.

Some limitations of this study should be addressed. First, the number of studies fulfilled the eligibility criteria and finally included in this study were limited. Among which 4 studies reported the polymorphism of rs36084323 (PD-1.1 G/A) (3 from Asians and 1 from Caucasians); 5 studies reported the



**Figure 2.** Forest plot describing the association between rs36084323 (PD-1.1 G/A) polymorphism and RA risk under the allele contrast model (A vs G).

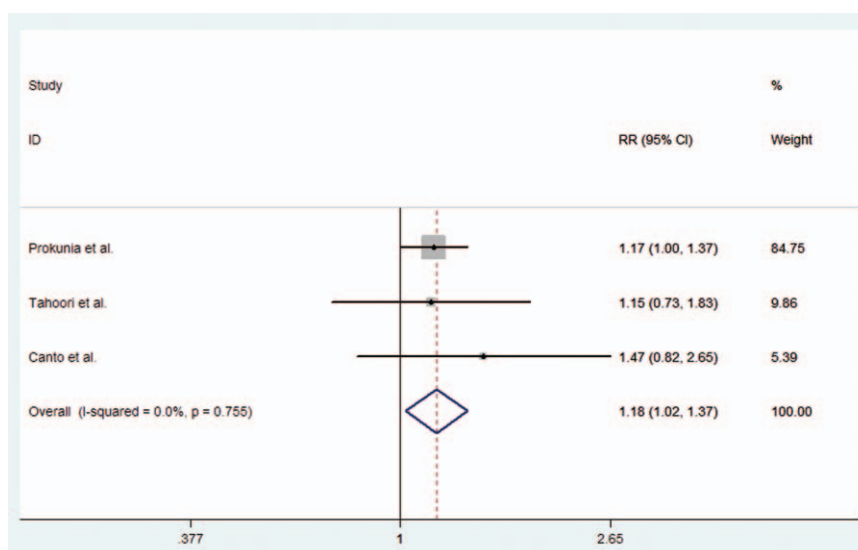


Figure 3. Forest plot describing the association between rs11568821 (PD-1.3G/A) polymorphism and RA risk under the allele contrast model (A vs G).

polymorphism of rs11568821 (PD-1.3 G/A) (2 from Asians and 3 from Caucasians); 3 studies reported the polymorphism of rs2227981 (PD-1.5 C/T) (all from Asians). This could not provide sufficient statistical power to study the exact effect of SNPs in *PDCD1* gene, especially in different ethnic groups, so our analysis may have been underpowered. Second, confounding factors, publication bias, and heterogeneity may have distorted the results. Furthermore, we primarily collected data about the rs2227982 (PD-1.9 C/T) polymorphism and the RA risk, but only 2 studies were eligible and they were from different ethnicity so thus it were not included in our study.

In conclusion, we conducted a meta-analysis of all the eligible studies related to the rs36084323 (PD-1.1 G/A), rs11568821

(PD-1.3 G/A), and rs2227981 (PD-1.5 C/T), and susceptibility to RA. The results show that no significant relationships were observed between rs36084323 (PD-1.1 G/A) and rs2227981 (PD-1.5 C/T) polymorphisms and RA risk, neither in Caucasians nor Asians, while rs11568821 (PD-1.3 G/A) was observed to be significantly associated with risk of RA in Caucasians (OR = 1.18, 95% CI = 1.02–1.37). The mutant A allele in rs11568821 (PD-1.3 G/A) polymorphism represents a higher risk of RA in Caucasians. However, as a limited number of eligible studies were included in this work, the reported results should be cautiously interpreted. For the purpose of obtaining more reliable results, it is necessary to conduct better-designed studies based on larger sample sizes in the future.

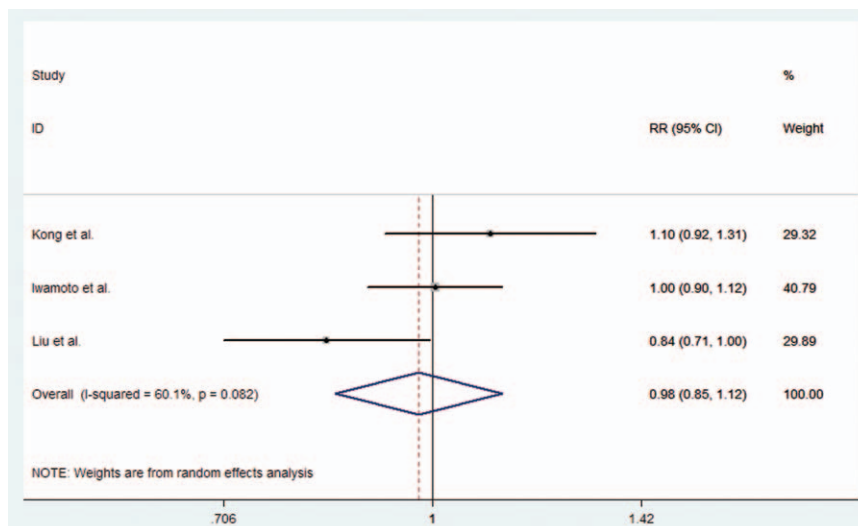


Figure 4. Forest plot describing the association between rs2227981 (PD-1.5C/T) polymorphism and RA risk under the allele contrast model (T vs C).

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