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REVIEW

Promoter polymorphism (−590, T/C) of interleukin 4 (*IL4*) gene is associated with rheumatoid arthritis: An updated meta-analysis

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Abstract Rheumatoid arthritis (RA) is a chronic disease. It causes chronic inflammation of the joint. Recent studies suggested that interleukin 4 (IL4) contributes to susceptibility and severity of rheumatoid arthritis (RA). Especially, it was reported that promoter polymorphism (−590, T/C) of *IL4* gene has been associated with susceptibility of RA. The aim of present study was to investigate whether the promoter polymorphism (−590, T/C) of *IL4* gene is associated with the susceptibility of RA using meta-analysis. And in order to perform meta-analysis, comprehensive meta analysis program was used. Genetic models (co-dominant, dominant, recessive, and allele) were used to determine odds ratios (ORs), 95% confidence intervals (CIs), and *P* values. Nine case-control studies with case and control design were included in this meta-analysis. Overall, meta-analysis revealed a strong association with susceptibility of RA [OR = 1.303, 95% CI = 1.093–1.554, $P = 0.003$ in allele model (C vs. T); OR = 1.247, 95% CI = 1.054–1.474, $P = 0.010$ in dominant model (CC vs. CT + TT); OR = 2.148, 95% CI = 1.263–3.651, $P = 0.005$ in recessive model (CC + CT vs. TT)]. Our data demonstrated that promoter polymorphism (−590, T/C) of *IL4* gene may be contributed to susceptibility of RA. However, more studies with a larger sample size are needed to provide more precise evidence.

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1. Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disorder and the most common inflammatory arthritis (Lee and Weinblatt, 2001; Antonisamy et al., 2015). The incidence of RA in 2008 was estimated to be 42/100,000 in South Korea (Sung et al., 2013). And the annual incidence in Norway was 28.7/100,000 (Riise et al., 2000) and 44.6/100,000 in Rochester, Minnesota (Doran et al., 2002).

RA is the most common autoimmune disease. The adaptive T-cell response interactions with environmental factors such as smoking lead to a systemic autoantibody response and it results in the synovial inflammatory process (Pablos and Canete, 2013). In these inflammatory responses, many previous studies investigated the role of genetic factors. HLA has been regarded as an important genetic factor in RA risk (Ollier and MacGregor, 1995). *IL27* gene polymorphism was associated with susceptibility of RA in Chinese (Yan et al., 2015). Recent meta-analysis showed the association between *CCR6* polymorphism and RA (Cheng et al., 2015).

IL4 gene is located at 5q31.1 and encodes interleukin 4 (http://www.ncbi.nlm.nih.gov). IL4 improves anti-inflammatory effect and suppresses several pro-inflammatory cytokines and systemic IL4 treatment protects the cartilage and bone destruction in established murine type II collagen-induced arthritis (Joosten et al., 1999). Also, IL4 could be used for the treatment of RA in association with anti-TNF alpha or anti-IL1 beta (Meyer, 2003). Genetic polymorphism of *IL4* also has an association with RA. *IL4* promoter polymorphism may be a genetic risk factor for RA severity (Pawlik et al., 2005). Previous study also suggested that the promoter polymorphism may be helpful for assessing RA severity (joint erosion and anti-CCP) and TT genotype of polymorphism (−590) showed a significant decrease of IL4 level in serum (Moreno et al., 2007).

Though the roles of *IL4* polymorphisms in RA have been reported in Chinese (Li et al., 2014) or White participants, the results has been controversial. In this study, we performed a meta-analysis on all eligible case-control studies to clarify the association between *IL4* polymorphism (−590) and susceptibility to RA.

2. Materials and methods

2.1. Search strategy and data extraction

We firstly found the meta-analysis studies between *IL4-590* polymorphism and RA. And electronic database including pubmed, embase, google of scholar, and Korean Studies Information Service System (KISS) were investigated up to June 2015. In order to select eligible studies about *IL4-590* polymorphism and RA. The keywords to find eligible studies were used: "interleukin 4", "IL4", or "cytokine", AND "polymorphism" or "SNP" AND "−590" or "rs2243250" AND "RA". The data of first author's name, year of publication, country, sample size of RA and control, genotype frequencies of *IL4-590* polymorphism in RA and control were extracted from the final selected studies.

2.2. Inclusion criteria

Studies were included if they met the following criteria: (1) evaluated the association between the IL4 polymorphism (−590, T/C) and RA; (2) used a case-control study design; (3) contained sufficient published data for the estimation of an odds ratio (OR) with a 95% confidence interval (CI).

2.3. Statistical analysis

Hardy–Weinberg equilibrium (HWE) in the control group of include studies was evaluated by the Chi-square test. Meta-analysis and sensitivity analysis were used by the Comprehensive Meta-analysis software (Corporation, NJ, USA). The pooled p value, OR, and 95% CI were used to assess the strength of association between risk of RA and *IL4-590* polymorphism (Kim et al., 2013; Seok et al., 2014). The meta-analysis was performed while omitting each study one at a time to examine the influence of each study on the pooled OR. In order to assess heterogeneity among the studies, a χ^2-test-based Q statistic test and I squared test were done. The random-effects Mantel–Haenszel method was adopted if the result of the Q test was $P < 0.05$ or I squared value was $>50\%$, which indicated the statistically significant heterogeneity between the studies. Otherwise, the fixed-effects

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

Study	Country	RA/Control (*n*)	Genotyping method	RA			Control			RA		Control		HWE in control
				C/C	C/T	T/T	C/C	C/T	T/T	C	T	C	T	
Trajkov et al. (2009)	Macedonia	85/286	Sequencing	47	37	1	95	187	4	131	39	377	195	**<0.001**
Nuñez et al. (2008)	Spain	599/540	TaqMan	398	179	22	375	155	10	975	223	905	175	0.185
Moreno et al. (2007)	Colombian	102/102	PCR-RFLP	39	48	15	49	48	5	126	78	146	58	0.11
Pawlik et al. (2005)	Poland	94/102	PCR-RFLP	62	28	4	74	26	2	152	36	174	30	0.87
Plenge et al. (2005)	Sweden	1503/875	Sequenom	940	507	56	584	253	38	2387	619	1421	329	0.12
Plenge et al. (2005)	North America	835/847	Sequenom	594	219	22	571	254	22	1407	263	1396	298	0.38
Cantagrel et al. (1999)	France	107/68	PCR-RFLP	63	41	3	82	36	0	167	47	200	36	0.05
Emonts et al. (2011)	Netherland	372/460	Sequencing	267	91	14	339	112	9	625	119	790	130	0.94
Hussein et al. (2013)	Egypt	172/172	PCR-RFLP	96	56	20	123	46	3	248	96	292	52	0.58
Li et al. (2014)	China	752/798	PCR-RFLP	481	218	53	575	207	16	1180	324	1357	239	0.60
Canet et al. (2015)	Spain	1239/1229	KASPar	859	325	34	863	275	34	2043	393	2001	343	**0.037**

RA = rheumatoid arthritis, *n* = number of subjects.
Bold number indicates significant difference.

Table 2 Overall analysis between *IL4*-590 polymorphism and susceptibility of RA in nine studies.

Genetic comparison	Association		Heterogeneity		Model	Publication bias
	OR (95% CI)	*P*	*P*	I^2		Egger's test
C vs. T	1.303 (1.093–1.554)	**0.003**	<0.001	75.46	Random	0.18
C/C vs. C/T + T/T	1.247 (1.054–1.474)	**0.010**	0.006	62.75	Random	0.22
C/C + C/T vs. T/T	2.148 (1.263–3.651)	**0.005**	<0.001	72.26	Random	0.09
C/C vs. C/T	1.128 (1.025–1.241)	**0.014**	0.100	40.28	Fixed	0.37
C/C vs. T/T	2.272 (1.313–3.931)	**0.003**	<0.001	73.55	Random	0.10

Rheumatoid arthritis (RA), odds ratio (OR), confidence interval (CI), number of subjects (*n*).
Bold numbers indicate significant association with RA.

Mantel–Haenszel method was adopted. And Begg's funnel plot and Egger's test were performed to evaluate publication bias. For sensitivity analysis, the meta-analysis was performed subtracting each study to examine the influence of each study over and over again. The $P < 0.05$ was regarded as statistically significant.

3. Results

The present study performed the meta-analysis to assess relationship between promoter polymorphism (−590, T/C) of *IL4* gene and susceptibility of RA. Firstly, searching was conducted to find related studies from electronic databases according to search strategy. Eleven case and control studies about promoter polymorphism (−590, T/C) of *IL4* gene polymorphism (Ser326Cys) and susceptibility of RA were searched (Canet et al., 2015; Cantagrel et al., 1999; Emonts et al., 2011; Hussein et al., 2013; Li et al., 2014; Nunez et al., 2008; Moreno et al., 2007; Pawlik et al., 2005; Plenge et al., 2005; Trajkov et al., 2009). Among these studies, six studies (Cantagrel et al., 1999; Pawlik et al., 2005; Moreno et al., 2007; Nunez et al., 2008; Trajkov et al., 2009; Hussein et al., 2013) were analyzed by meta-analysis in 2013 (Song et al., 2013). However, there was an error in data by the meta-analysis in 2013. Song et al., 2013 reported results of meta-analysis between promoter polymorphism (−590, T/C) of *IL4* gene and susceptibility of RA. They included the data from the study (Cantagrel et al., 1999) in the meta-analysis They summarized that the genotype frequencies (C/C:C/T:T/T) of promoter polymorphism (−590, T/C) of *IL4* gene in the control group were 32:36:0, but original data of the study (Cantagrel et al., 1999) is 82:36:0. In meta-analysis between specific polymorphisms and susceptibility of diseases, it was important to search eligible studies and extract exact data. So, this updated meta-analysis was performed.

Table 1 shows characteristics of eligible studies included in the meta-analysis. The first author's name, year of publication, country, sample size, and genotype frequencies of *IL4*-590 polymorphism in RA patients and controls were extracted. Among eleven studies, studies by Trajkov et al., 2009 and Canet et al., 2015 were excluded in the meta-analysis because HWEs of genotype distribution of *IL4*-590 polymorphism in the control group was $p < 0.05$. Table 2 and Fig. 1 presents the results of meta-analysis between *IL4*-590 polymorphism and susceptibility of RA in nine studies. In all models, *IL4*-590 polymorphism revealed the significant association with susceptibility of RA (random model, OR = 1.303, 95% CI = 1.093–1.554, $P = 0.003$ in allele; random model, OR = 1.247, 95% CI = 1.054–1.474, $P = 0.010$ in dominant; random model, OR = 2.148, 95% CI = 1.263–3.651, $P = 0.005$ in recessive; Fixed model, OR = 1.128, 95% CI = 1.025–1.241, $P = 0.014$ in codominant 1; Random model, OR = 2.272, 95% CI = 1.313–3.931, $P = 0.003$ in codominant 2). Sensitivity analysis confirmed the stability of the results of meta-analysis (data not shown) and no publication bias was found in the present meta-analysis. These results indicate that promoter polymorphism (−590, T/C) of *IL4* gene polymorphism is related to susceptibility of RA (Table 2 and Fig. 1).

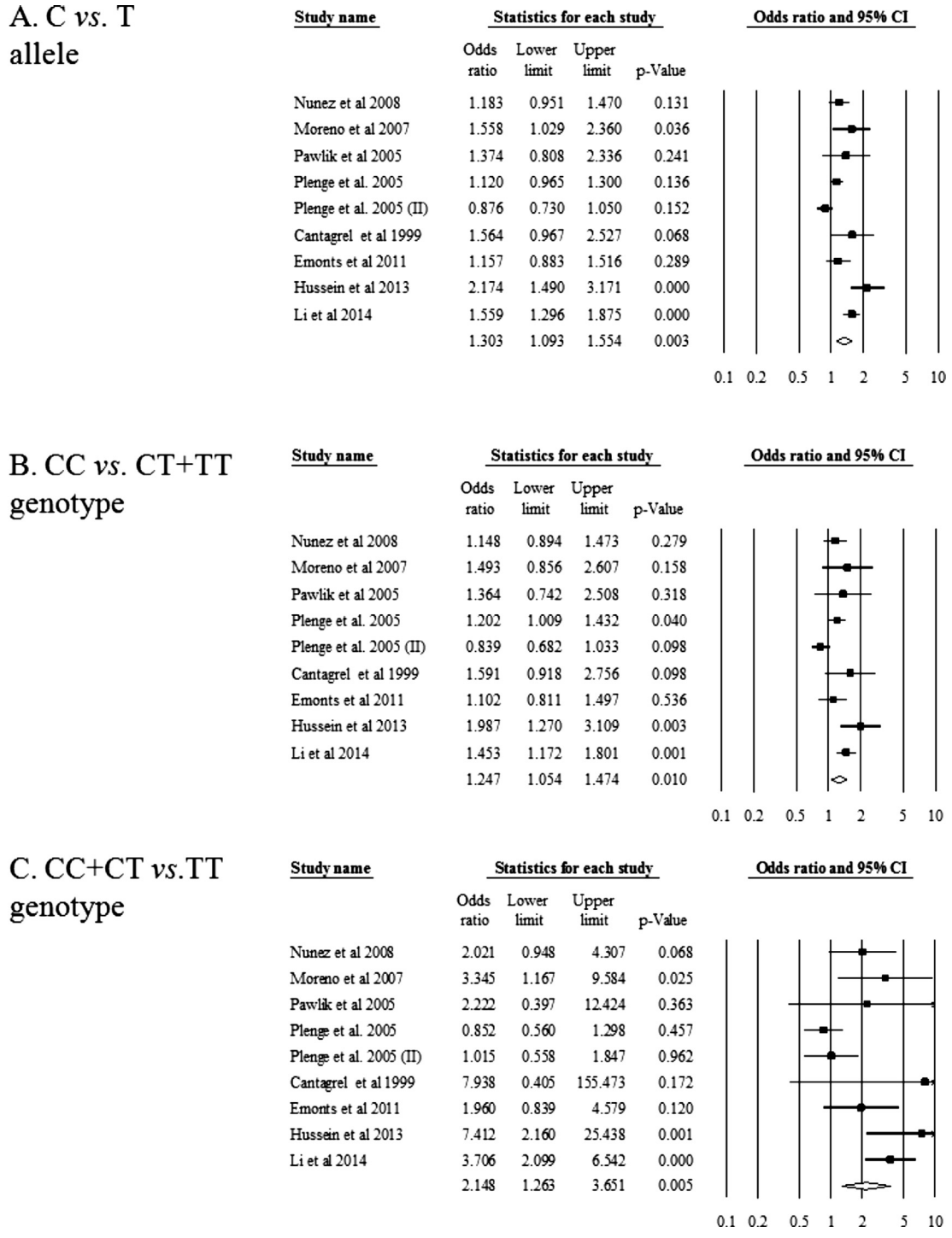

Figure 1 Odds ratio and 95% CI of individual and pooled data for the *IL4* polymorphism (−590) and susceptibility of RA. A: C allele vs. T allele; B: C/C genotype vs. C/T genotype + T/T genotype; C: C/C genotype + C/T genotype vs. T/T genotype.

4. Discussion

Many factors such as gene, cytokine, inflammatory mediators, adhesion molecules, and so on involve in the pathophysiology of RA. Among them, many genetic factors have been identified due to advances in genetic methods (Lee and Weinblatt, 2001). In this study, we focused on the genetic factor of RA and carried out meta-analysis to investigate the relation between *IL4* polymorphism and the risk of developing RA.

In the present study, we could find significant associations in allele, dominant, and recessive models. The results of this meta-analysis are consistent with the results of a previous meta-analysis (Canet et al., 2015). Among these, only the study by Li et al. (2014) involves Asian population (Chinese). According to NCBI database, genotype frequency in Chinese is 0.023 (C/C), 0.395 (C/T), and 0.581 (T/T) and allele frequency in Chinese is 0.221 (C) and 0.779 (T). On the other hand, genotype and allele frequencies in White are definitely

different. According to NCBI database, genotype frequency in European is 0.743 (C/C), 0.239 (C/T), and 0.018 (T/T) and allele frequency in Chinese is 0.863 (C) and 0.137 (T). As shown in Table 1, genotype and allele frequencies in previous studies are similar to those in NCBI database. Interestingly, the genotypes and allele frequencies in 2014 by Li et al. (2014) are similar to those of European rather than those of Asian according to NCBI database. Previous study reported that the incidence and prevalence of RA showed different trends according to ethnicity. In Korea, the prevalence of RA in 2008 was estimated to be 0.27% (Sung et al., 2013). One study on rural African had found only 14 cases of RA in about 520,000. The prevalence of RA was 0.0026% (Brighton et al., 1988). In contrast, the prevalence of RA in a Chippewa Band (American Indian) reached to 5.3–6.8% (Harvey et al., 1981). A study in Norway reported that the prevalence of RA was 0.47% in 1994 (Riise et al., 2000). In United Kingdom, the prevalence of RA is 1.16% in women and 0.44% in men (Symmons et al., 2002). The prevalence of RA in the urbanized Chinese of Hong Kong was 0.35% (Lau et al., 1993). Thus, previous studies showed the significant geographic variations of RA occurrence and difference of prevalence according to ethnicity. These results suggest an association of RA with ethnicity and genetic factors.

5. Conclusion

In conclusion, our meta-analysis study showed that *IL4* polymorphism was associated with RA. However, the limitation of our study is that there was not enough data on other ethnicities. We could not find the studies on African population and the number of studies on Asian was only one. In spite of these limitation, our meta-analysis provided evidence of the association between *IL4* polymorphism and risk of RA. It is well known that early diagnosis and treatment of RA could lead to favorable outcomes. Therefore, early diagnosis and preventive treatment by detecting the susceptibility to RA in gene level would play a major role in improving the prognosis of RA. Many previous association studies revealed the association between *IL4* polymorphism and RA and our present meta-analysis strengthened the relationship. If further studies will be performed in more population, promoter polymorphism (−590, T/C) of *IL4* gene could be a useful marker for the early diagnosis and treatment of RA.

Author disclosure statement

No competing financial interests exist.

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