No association of interleukin-1 receptor antagonist VNTR polymorphism and rheumatoid arthritis susceptibility: a meta-analysis

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Abstract

Background & objectives

Interleukin-1 receptor antagonist (IL-1Ra) is a natural anti-inflammatory molecule that blocks the action of IL-1 signaling. A variable-number tandem repeat polymorphism (VNTR) in IL-1Ra gene (IL-1RN) intron 2 has been reported to be associated with rheumatoid arthritis (RA), with inconsistent results. Here, we perform a meta-analysis to assess the common effect size of this polymorphism on RA susceptibility.

Methods

Case-control studies on IL-1RN VNTR association with RA were searched up to January 2010. The effect summary odds ratio (OR) and 95% confidence intervals was obtained by meta- analysis.

Results

A total of 15 studies involving in IL-1RN VNTR with RA susceptibility were included in this meta-analysis. No association between A2/A2 genotype and risk of RA to other genotypes (odds ratio [OR], 0.96; 95% CI =0.75-1.24, p=0.77), and between A2 allele and risk of RA (OR, 0.98; 95% CI=0.83-1.16, p=0.85), were demonstrated in the total meta-analysis. In both Asian and European subgroups, the overall effect of A2/A2 genotype and A2 allele also showed no significant difference.

Conclusion

This meta-analysis demonstrates that the IL-1RN VNTR polymorphism is not related to susceptibility to RA.

Key words

Interleukin-1 receptor antagonist, polymorphism, rheumatoid arthritis, susceptibility, meta-analysis

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Received on December 18, 2009; accepted in revised form on March 22, 2010.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease, characterised by chronic inflammation of multiple joints and synovial inflammation, leading to the destruction and disability of joints (1). It has been evidenced that interlukin-1 (IL-1), a key mediator of inflammation and tissue destruction in RA, plays a central role in RA pathogenesis. The interleukin-1 receptor antagonist (IL-1Ra) is a member of the IL-1 family that binds to IL-1 receptors without inducing any intracellular signal transduction (2). Therefore, it acts as a competitive inhibitor of IL-1 bioactivity in inflammatory disorders. In several experimental models of arthritis, exogenous administration of IL-1Ra or increasing local IL-1Ra level in the synovium by gene delivery, could inhibit or prevent the severity or recurrence of arthritis (3-6). Furthermore, IL-1Ra knockout mice spontaneously develop inflammatory arthritis similar to human RA (7). Consistent with these observations, anakinra, a recombinant IL-1Ra, provides clinical benefits in patients with RA (8, 9). These findings suggest IL-Ra is a strong candidate gene of RA.

A variable numbers of an 86-bp tandem repeat (VNTR) polymorphism in human IL-1Ra gene (IL-1RN) intron 2 has been found to be functionally associated with IL-1Ra expression in several studies (10-12). The potential contribution of this polymorphism to RA susceptibility was also examined in several studies; however, the results were totally inconsistent (13-27). In Spanish and Chinese population, the two-repeat allele (IL-1RN*2) was reported to be associated with a significantly increased risk of RA (20, 25). However, these results could not be reasserted in the same population by other authors (16, 18, 27). In contrast to these studies, a protective effect of this allele in the pathogenesis of RA has also been implicated in Korean population (19). Furthermore, the distribution of IL-1RN*3, not IL-1RN*2 was higher in RA patients than that of the normal control in Swedes and Italians (17, 23).

A meta-analysis can summarise the results from different studies by producing a single estimate of the major effect with enhanced precision (28). Here, we performed a meta-analysis to study the association of IL-1RN VNTR and RA, and found there was no association of this polymorphism and RA.

Materials and methods

Identification of eligible studies

We performed an exhaustive search on studies that examined the association of the IL-1 RN VNTR polymorphism with RA. These studies were identified by extensive computer-based searches of the PubMed database, and the Cochrane library up to January 2010. References in the Medline-cited studies were reviewed to identify additional reports not indexed by Medline. "Interleukin-1 receptor antagonist", "IL-1 RN" "polymorphism", "rheumatoid arthritis" and "RA" were entered as both medical subject heading (MeSH) terms and text words. No restriction was placed on language, race, ethnicity or geographic area. Only data from full-published papers has been included in this meta-analysis.

Studies included in this meta analysis fulfilled the following requirements: 1) the diagnosis of RA was established using the American College of Rheumatology classification criteria for rheumatoid arthritis; 2) it should be case-control design; 3) it should be published in peer-reviewed journals as full papers, not an abstract or similar, up to January 2010; 4) it should be an original data (independent among studies) and should provide enough information to calculate the odds ratio (OR). We excluded the following: 1) studies that were not case-control approach, 2) studies in which the number of null and wild genotypes could not be ascertained, and 3) studies in which family members had been studied because their analysis is based on linkage considerations (the selecting process is shown in Supplemental Fig. 1).

Data extraction

Two investigators extracted standard information from independently abstracted data. For each study, the following information was extracted: first author, journal, year of publication,

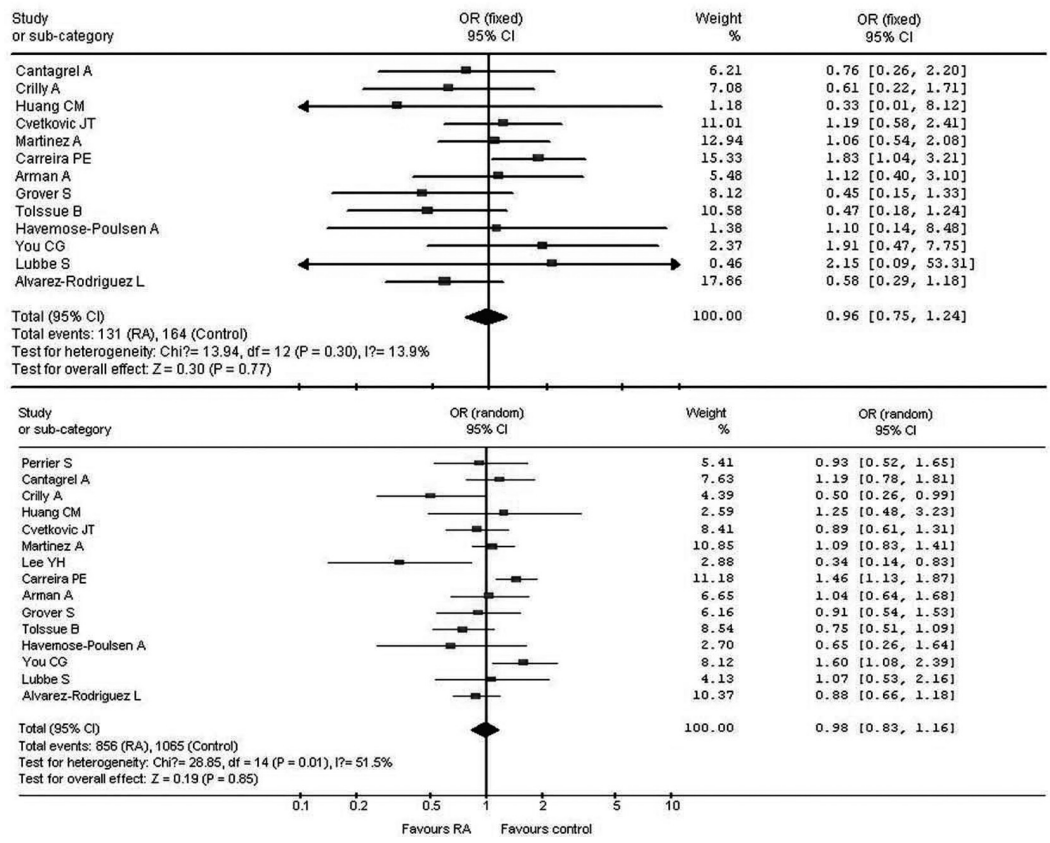
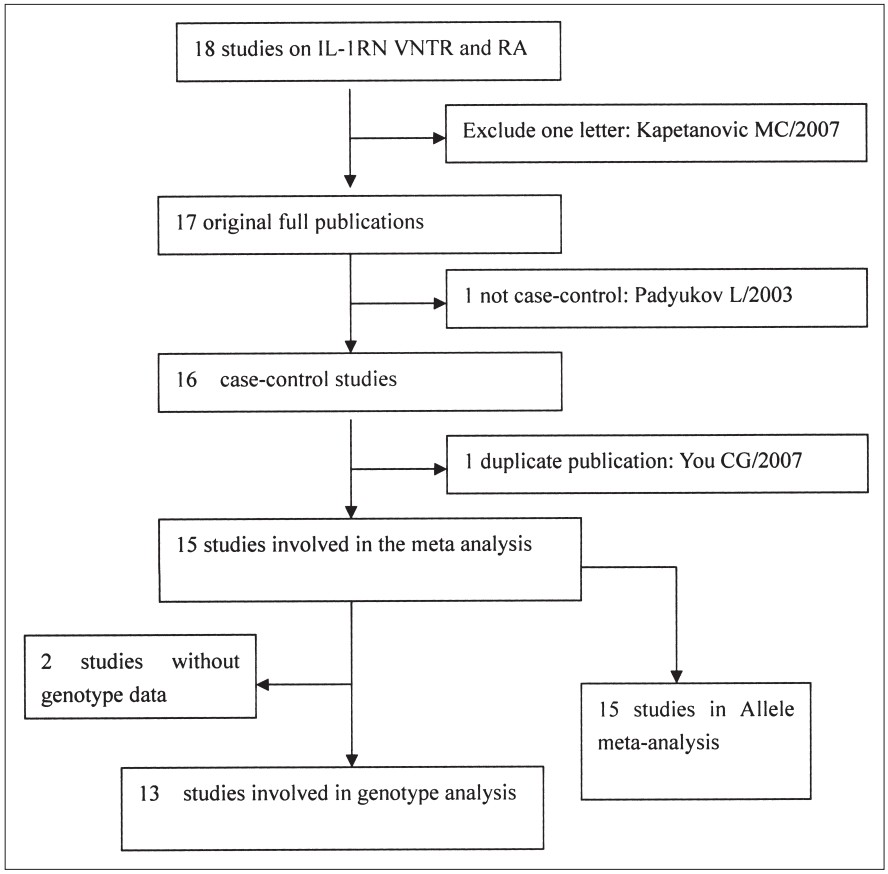


Fig. 1. Association between IL-1RN VNTR and the development of RA in all studies: A2/A2 versus other genotypes (top) and A2 versus other alleles (bottom). Aggregate OR, 95% CI of risk genotype, and risk allele also are given, along with the probability of heterogeneity of Cochran's Q-test. The weighting factor (weight %) used to calculate the aggregate OR, calculated from the inverse of the variance, is given for each study.



Supplemental Fig. 1. The literature review process of the meta-analysis.

racial descent of study population, demographics, matching, validity of the genotyping method, and the number of cases and controls for each IL-1RN genotype. The frequencies of the alleles were calculated for the respective study by the allele-counting method.

Evaluation of publication bias

To assess publication bias, we evaluated study quality by using a funnel plot. We constructed a funnel plot of effect size against its SE. The funnel plot should be asymmetric when there is publication bias and symmetric in the case of no publication bias. Because the funnel plot approach is limited by the requirement for a range of studies with varying size, we used Egger's linear regression test. Egger's test measures the funnel plot asymmetry on the natural logarithm scale of OR.

Statistical analysis

A chi-square test was used to determine whether observed frequencies of genotypes conformed to Hardy-Weinberg expectations (HWE). We used the Review Manager 4.2 software (The

Table I. Characteristics of individual studies included in the meta-analysis.

Author/year Author's conclusion	Population	Patients/ Control no.	Detailed characteristics of RA patients				Author's conclusions
			Mean age (y)	Female/ Male	Disease duration (y)	RF positive	
Perrier S/1998	French	43/100	ND	ND	ND	ND	NS
Cantagrel A/1999	French	108 /125	ND	ND	ND	ND	NS
Crilly A/2000	Briton	100/64	ND	80.0%	ND	ND	NS
Huang CM/2001	Chinese	104/103	ND	ND	ND	ND	NS
Cvetkovic JT /2002	Swede	154 /202	64.0 ± 20.3	72.7%	15.5 ± 9.7	94.1%	Allele A3 showed an increased frequency in patients
Martinez A/2003	Spanish	229/371	ND	ND	ND	ND	NS
Lee YH/2004	Korean	138/127	45 (16–75)	82.6%	ND	ND	A protective role of IL-1RN*2 in the pathogenesis of RA.
Carreira PE/2005	Spanish	441/287	ND	ND	ND	ND	IL1RN*2 has a role in determining susceptibility to RA
Arman A/2006	Turks	94/104	49	80.8%	8.8 (2-31)	65%	NS
Grover S/2006	Indian	107/111	45 (23-71)	86.9%	36.7 (17-58)	75%	NS
Tolssue B/2006	Italian	126/178	56.5 ± 14.1	91.3%	11.6±8.7	64.8%	IL-RN*3 was associated with RA
Havemose-Poulsen A /2007	Dane	23/25	30.0 ± 4.0	95.6%	ND	ND	NS
You CG/2007	Chinese	240/227	33.0 ± 12.0	69.6%	ND	ND	IL1RN*2 has a role in determining susceptibility to RA in female group
Lubbe S/2008	South African	138/98	50.7 ±11.4	87.9%	10.1 ±7.2	90.4%	NS
Alvarez-Rodriguez L/2009	Spanish	156/437	ND	68.2%	ND	59.7%	NS

ND: no data; NS: no significance.

Table II. The detail data of individual study involved in this meta-analysis.

Author/year (Ref)	Race	Genotype of control			Genotype of RA			Allele of control		Allele of RA	
		A2/A2	Other	total	A2/A2	Other	total	A2	other	A2	Other
Perrier S/1998 (13)	French	ND	ND	100	ND	ND	43	54	146	22	64
Cantagrel A/1999 (14)	French	9	116	125	6	102	108	57	193	56	160
Crilly A/2000 (15)	Briton	8	56	64	8	92	100	21	107	18	182
Huang CM/2001 (16)	Chinese	1	102	103	0	104	104	8	198	10	198
Cvetkovic JT /2002 (17)	Swede	18	184	202	16	138	154	79	325	55	253
Martinez A/2003 (18)	Spanish	23	348	371	15	214	229	189	553	124	334
Lee YH/2004 (19)	Korean	0	127	127	0	138	138	18	236	7	269
Carreira PE/2005 (20)	Spanish	18	269	287	48	393	441	120	454	245	637
Arman A/2006 (21)	Turk	8	96	104	8	86	94	43	165	40	148
Grover S /2006 (22)	Indian	11	100	111	5	102	107	36	186	32	182
Tolusso B/2006 (23)	Italian	17	161	178	6	120	126	100	256	57	195
Havemose-Poulsen A /2007 (24)	Dane	2	23	25	2	21	23	15	35	10	36
You CG/2007 (25)	Chinese	3	224	227	6	234	240	45	409	72	408
Lubbe S/2008 (26)	South African	0	98	98	1	137	138	14	182	21	255
Alvarez-Rodriguez L/2009 (27)	Spanish	46	391	437	10	146	156	266	608	21	255

ND: no data.

Cohrone, England) for meta-analysis. First, the within and the between-study variation or heterogeneity was examined by Cochran's Q-test. This heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. If the significant Q-statistic ($p<0.05$) indicated heterogeneity across studies, the overall or pooled OR was obtained by DerSimonian and Laird method in the random effect model, Otherwise, the Mantel-Haenszel method in the fixed effect model was selected.

Results

Studies included in the meta-analysis

Initially, a total of 18 relevant studies addressing the relationship of IL-RN polymorphism and susceptibility to RA were initially identified through an electronic database search and reference review. Two studies were excluded from the meta-analysis, because one study was not case-control design (29) and another was published as a letter (30). Furthermore, one study was excluded to avoid inclusion of duplicated data, because the same group of authors published the two studies at a very close period, with a similar number of patients and controls (25, 31). Therefore, a total of 15 studies were recruited in this meta-analysis. These 15 studies include 9 European, 5 Asian and 1 Latin American subject collections, with a total number of 2201 RA patients and 2559 controls, as summarised in Table I and Table II. Among the RA group, the frequency of A2/A2 genotype and A2 allele was 6.07% and 19.3%, respectively, whereas it was

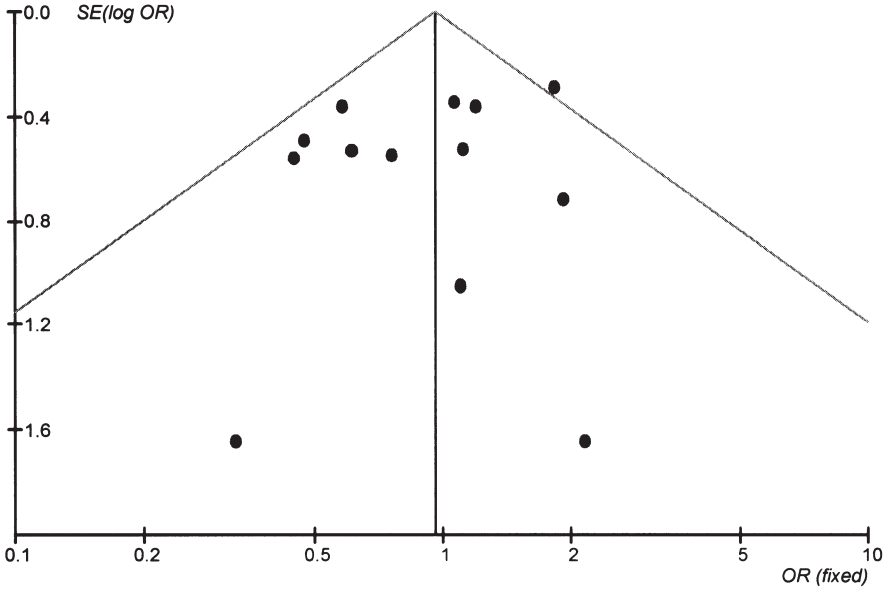


Fig. 2. Funnel plot analysis of all studies on IL-1RN VNTR and the development of RA. The results showed that all studies were evenly distributed within an inverse funnel shape around the total line (as indicated by the 95% CI lines).

6.67% and 20.8% in control group, without significant difference.

The finding of these 15 studies is controversial. Even in the same population of Spanish (18, 20, 27) and Chinese (16, 25), different studies produced different results. Among the 5 studies that reported a significant association of IL-1 RN VNTR with RA, 3 studies found that the A2 allele had a role in determining susceptibility to RA (19, 20, 25), whereas other 2 studies demonstrated the association of the A3 allele with RA (17, 23).

Study quality

The distribution of the genotype of the IL-1RN VNTR polymorphism in control groups was consistent with the HWE. One study had limitation with respect to the number of both RA patients and control (24). However, excluding the study did not materially affect the overall results (data not shown). There was no evidence of publication bias in this meta-analysis (Egger's regression test *p*-values >0.1). (The funnel plot is shown in Fig. 2)

The allele frequency of IL-1RN VNTR was extracted from all 15 studies (13-27). However, the genotype frequency was available from only 13 studies (14-18, 20-27). One study did not provide the genotype data (13), and in another study performed in Korean population by Lee *et al*. there was no A2/A2 genotype reported (19).

Evaluation of IL-1 RN VNTR polymorphism and association with RA

No significant association was found between the RA susceptibility and the A2/A2 genotype or the A2 allele in all studies (Table III, Fig. 1). The fixed effects odds ratio (OR) estimated for the risk of developing RA was 0.96 in A2/A2 homozygous patients compared with other genotypes combined (95% CI 0.75–1.24), without between-study heterogeneity (*p*=0.77). Meanwhile, the random effect OR estimated for the risk of developing RA was 0.98 in A2 allele patients compared with patients carrying other alleles (95% CI 0.83–1.16), with evidence of between-study heterogeneity (*p*=0.01; Table III, Fig. 1).

To evaluate the race-specific effect, we divided the population by ethnicity. There was no considerable heterogeneity across the Asian studies (*p*=0.35). The overall OR for the A2/A2 genotype in Asians was 0.85 (95% CI 0.46–1.59, *p*=0.62; Table II). The overall OR for the A2 allele also showed the similar magnitude (OR 0.99, 95% CI 0.64–1.53), without statistical significance (*p*=0.96; Table III).

In European studies, the random effects OR estimated for the risk of developing RA was 0.98 in A2/A2 homozygous patients compared with other genotypes combined (95% CI 0.75–1.29), without between-study heterogeneity (*p*=0.17). Meanwhile, the random effect OR estimated for the risk of developing RA was 0.96 in A2 allele patients compared with patients carrying other alleles (95% CI 0.79–1.17), with evidence of between-study heterogeneity (*p*=0.02; Table III).

Discussion

IL-1Ra modulates the biological activity of the proinflammatory cytokine IL-1 and plays an essential role in the pathophysiology of inflammatory process such as RA. However, there are contradictory data regarding the association between IL-1RN and RA risk.

Table. III. The meta-analysis of IL-RN VNTR polymorphism and the development of RA.

Polymorphic sites	Ethnic group	no. of studies	Sample Size		Model	Test of association		
			RA	Control		Z	*p*-value	OR 95% CI
A2/A2 genotype	All studies	13	2020	2332	Fixed	0.30	0.30	0.96 (0.75-1.24)
	Asian	4	545	545	Fixed	0.50	0.35	0.85 (0.46-1.59)
	European	8	1337	1689	Fixed	0.15	0.17	0.98 (0.75-1.29)
A2 Allele	All studies	15	4402	5118	Random	0.23	0.01	0.98 (0.83-1.16)
	Asian	5	1366	1344	Random	0.04	0.03	0.99 (0.64-1.53)
	European	9	2760	3578	Random	0.38	0.02	0.96 (0.79-1.17)

This discrepancy among these different studies is not surprising. There are reasons for the contradictory results: small genetic effects, limited number involved, disease or population heterogeneity, as well as the extent and degree of linkage disequilibrium between the marker tested and the causal variants, etc. (28). This is also the reason why we performed the meta-analysis to confirm the relationship of IL-1RN and RA. Our meta-analysis concludes that there is no association between this polymorphism and RA, both in the overall population samples and ethnicity-divided studies (Fig. 1 and Table III).

The detailed reasons why there is no association of IL-1RN VNTR with RA are unknown. One possible explanation could be linkage disequilibrium of VNTR with some other more relevant, but as-yet unidentified, allele or alleles of genes within the IL-1 cluster (32). The direct evidence was several genetic studies performed in multiplex RA families, which found the linkage of genes in the IL-1 region with the disease (33, 34). In fact, increasing evidences suggest the non-causal role of IL-1RN VNTR in RA risk. First, in respect to the gene structure, IL-1Ra gene is located in chromosome 2, in close linkage with the IL-1 gene within a 430KB region (35). Second, several functional SNPs were identified in IL-Ra gene recently. One SNP, rs4251961, has been reported in weak linkage disequilibrium with VNTR polymorphism and strongly associated with IL-1Ra levels (36). This SNP might be potential candidate polymorphism and allow the investigation of the causal direction of associations between IL-1RN and RA risk. Third, though IL-RN VNTR was previously considered a functional mutation, the studies concerning the association of IL-RN VNTR and IL-Ra protein levels are also totally discrepant. Early studies demonstrated increased secretion of IL-1Ra protein from mononuclear cells of IL-1RN*2 carriers (10-12), whereas later studies produced reverse results (23, 37-39). These evidences implicated that there was a functional polymorphism at the IL-1 cluster that might be linked to IL-1RN*2, resulting in the generation of a proinflammatory environment.

Insufficient sample size, both for RA patients and control groups in these original studies involved in our meta-analysis, might be another possible reason for negative results, which also might underpowered our analysis. Of all 15 studies included in the meta-analysis, only five studies recruited more than 200 RA patients or controls. The average number of RA patients and controls in each study is just 146 and 171, respectively.

Due to the data limitations, additional analyses can not be performed in different clinical subgroups, such as the response to immunotherapy. Recently, several studies indicated that patients carrying IL-1RN A2 allele were resistant to methotrexate (23) or anti-TNF treatment (29). This has two important clinical implications. First, with respect to pharmacogenomics, polymorphisms may influence the balance of pro- and anti-inflammatory cytokines that trigger the course of RA. Second, form the perspective of clinical therapeutics, if multiple-center studies with larger patient groups can define the issue, patients who carry IL-1a A2 allele can avoid the cost and side-effect of unreasonable immunotherapy.

Conclusion

This meta-analysis concludes that IL-1RN VNTR is not associated with the RA risk. However, there is clearly a need to confirm our data in a larger RA cohort or in a family-based study. Future study should also focus on the relationship of this polymorphism and the response of immunotherapy, to verify their eventual practical usefulness in clinical practice.

Acknowledgment

We are grateful to Dr Yong Du (University of Texas Southwestern Medical School at Dallas) for his valuable comments and kind assistance in revising this paper.

References

1. FURUZAWA-CARBALLEDA J, MACIP-RODRÍGUEZ PM, CABRAL AR: Osteoarthritis and rheumatoid arthritis pannus have similar qualitative metabolic characteristics and pro-inflammatory cytokine response. *Clin Exp Rheumatol* 2008; 26: 554-60.
2. AREND WP, GABAY C: Physiologic role of interleukin-1 receptor antagonist. *Arthritis Res* 2000; 2: 245-8.
3. VAN DE LOO FA, JOOSTEN LA, VAN LENT PL, ARNTZ OJ, VAN DEN BERG WB: Role of interleukin-1, tumor necrosis factor alpha, and interleukin-6 in cartilage proteoglycan metabolism and destruction. Effect of in situ blocking in murine antigen- and zymosan-induced arthritis. *Arthritis Rheum* 1995; 38: 164-72.
4. BAKKER AC, JOOSTEN LA, ARNTZ OJ *et al*.: Prevention of murine collagen-induced arthritis in the knee and ipsilateral paw by local expression of human interleukin-1 receptor antagonist protein in the knee. *Arthritis Rheum* 1997; 40: 893-900.
5. MAKAROV SS, OLSEN JC, JOHNSTON WN *et al*.: Suppression of experimental arthritis by gene transfer of interleukin 1 receptor antagonist cDNA. *Proc Natl Acad Sci USA* 1996; 93: 402-6.
6. OTANI K, NITA I, MACAULAY W, GEORGESCU HI, ROBBINS PD, EVANS CH: Suppression of antigen-induced arthritis in rabbits by *ex vivo* gene therapy. *J Immunol* 1996; 156: 558-62.
7. HORAI R, SAIJO S, TANIOKA H *et al*.: Development of chronic inflammatory arthropathy resembling rheumatoid arthritis in interleukin-1 receptor antagonist-deficient mice. *J Exp Med* 2000; 191: 313-20.
8. COHEN S, HURD E, CUSH J *et al*.: Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four–week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46: 614-24.
9. FIOCCO U, VEZZU M, COZZI L, TODESCO S: IL-1Ra (recombinanthuman IL-1 receptor antagonist) in the treatment of rheumatoid arthritis: the efficacy. *Reumatismo* 2004; 56: 62-73.
10. DANIS VA, MILLINGTON M, HYLAND VJ, GRENNAN D: Cytokine production by normal human monocytes: inter-subject variation and relationship to an IL-1 receptor antagonist (IL-1Ra) gene polymorphism. *Clin Exp Immunol* 1995; 99: 303-10.
11. STRANDBERG L, LORENTZON M, HELLQVIST A *et al*.: Interleukin-1 system gene polymorphisms are associated with fat mass in young men. *J Clin Endocrinol Metab* 2006; 91: 2749-54.
12. HURME M, SANTILLA S: IL-1 receptor antagonist (IL-1Ra) plasma Levels are coordinately regulated by both IL-1Ra and IL-1beta genes. *Eur J Immunol* 1998; 28: 2598-602.
13. PERRIER S, COUSSEDIERE C, DUBOST JJ, ALBUISSON E, SAUVEZIE B: IL-1 receptor antagonist (IL-1RA) gene polymorphism in Sjögren's syndrome and rheumatoid arthritis. *Clin Immunol Immunopathol* 1998; 87: 309-13.
14. CANTAGREL A, NAVAUX F, LOUBET-LESCOULIE P *et al*.: Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms: relationship to occurrence and severity of rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1093-100.
15. CRILLY A, MAIDEN N, CAPELL HA, MADHOK R: Predictive value of interleukin 1 gene

polymorphisms for surgery. *Ann Rheum Dis* 2000; 59: 695-9.
16. HUANG CM, TSAI FJ, WU JY, WU MC: Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in rheumatoid arthritis. *Scand J Rheumatol* 2001; 30: 225-8.
17. CVETKOVIC JT, WALLBERG-JONSSON S, STEGMAYR B, RANTAPAA-DAHLQVIST S, LEFVERT AK: Susceptibility for and clinical manifestations of rheumatoid arthritis are associated with polymorphisms of the TNF-alpha, IL-1beta, and IL-1Ra genes. *J Rheumato* 2002; 29: 212-9.
18. MARTINEZ A, PASCUAL M, PASCUAL-SALCEDO D, BALSA A, MARTIN J, DE LA CONCHA EG: Polymorphisms in Spanish rheumatoid arthritis patients: an association and linkage study. *Genes Immun* 2003; 4: 117-21.
19. LEE YH, KIM HJ, RHO YH, CHOI SJ, JI JD, SONG GG: Interleukin-1 receptor antagonist gene polymorphism and rheumatoid arthritis. *Rheumatol Int* 2004; 24: 133-6.
20. CARREIRA PE, GONZALEZ-CRESPO MR, CIRUELO E *et al*.: Polymorphism of the interleukin-1 receptor antagonist gene: a factor in susceptibility to rheumatoid arthritis in a Spanish population. *Arthritis Rheum* 2005; 52: 3015-9.
21. ARMAN A, YILMAZ B, COKER A, INANC N, DIRESKENELI H: Interleukin-1 receptor antagonist (IL-1RN) and interleukin-1B gene polymorphisms in Turkish patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2006; 24: 643-8.
22. GROVER S, TANDON S, MISRA R, AGGARWAL A: Interleukin-1 receptor antagonist gene polymorphism in patients with rheumatoid arthritis in India. *Indian J Med Res* 2006; 123: 815-20.
23. TOLUSSO B, PIETRAPERTOSA D, MORELLI A *et al*.: IL-1B and IL-1RN gene polymorphisms in rheumatoid arthritis: relationship with protein plasma levels and response to therapy. *Pharmacogenomics* 2006; 7: 683-95.
24. HAVEMOSE-POULSEN A, SØRENSEN LK, ENDTZEN K, HOLMSTRUP P: Polymorphisms within the IL-1 gene cluster: effects on cytokine profiles in peripheral blood and whole blood cell cultures of patients with aggressive periodontitis, juvenile idiopathic arthritis, and rheumatoid arthritis. *J Periodontol* 2007; 78: 475-92.
25. YOU CG, LI JF, XIE XD, ZHU Y, LI PQ, CHEN YR: Association of interleukin-1 genetic polymorphisms with the risk of rheumatoid arthritis in Chinese population. *Clin Chem Lab Med* 2007; 45: 968-71.
26. LUBBE S, TIKLY M, VAN DER MERWE L, HODKINSON B, RAMSAY M: Interleukin-1 receptor antagonist gene polymorphisms are associated with disease severity in Black South Africans with rheumatoid arthritis. *Joint Bone Spine* 2008; 75: 422-5.
27. ALVAREZ-RODRIGUEZ L, CARRASCO-MARIN E, LOPEZ-HOYOS M *et al*.: Interleukin-1RN gene polymorphisms in elderly patients with rheumatic inflammatory chronic conditions: Association of IL-1RN*2/2 genotype with polymyalgia rheumatica. *Hum Immunol* 2009; 70: 49-54.
28. YONG DU, QING WU, HUA L *et al*.: Association of angiotensin I-converting enzyme gene insertion/deletion polymorphism and IgA nephropathy: A meta-analysis. *Am J Nephrol* 2006; 26: 511-18.
29. PADYUKOV L, LAMPA J, HEIMBURGER M *et al*.: Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. *Ann Rheum Dis* 2003; 62: 526-9.
30. KAPETANOVIC MC, LINDQVIST E, STURFELT G, SAXNE T, TRUEDSSON L, EBERHARDT K: The impact of IL-1Ra and MBL gene polymorphisms on joint damage after 5 and 10 years in patients with early rheumatoid arthritis. *J Rheumatol* 2007; 34: 894-5.
31. YOU CG, YIN YS, XIE XD, JU J, WANG ZP, CHEN YR: Sex influences on the penetrance of IL-1beta and IL-1RN genotypes for rheumatoid arthritis in the Chinese population. *J Int Med Res* 2007; 35: 323-8.
32. COX A, CAMP NJ, NICKLIN MJ, DI GIOVINE FS, DUFF GW: An analysis of linkage disequilibrium in the interleukin-1 gene cluster, using a novel grouping method for multiallelic markers. *Am J Hum Genet* 1998; 62: 1180-8.
33. BARRERA P, FAURE S, PRUD'HOMME JF *et al*.: European genetic study on rheumatoid arthritis:is there a linkage of the interleukin-1 (IL-1), IL-10 or IL-4 genes to RA? *Clin Exp Rheumatol* 2001; 19: 709-14.
34. COX A, CAMP NJ, CANNINGS C *et al*.: Combined sib-TDT and TDT provide evidence forlinkage of the interleukin-1 gene cluster to erosive rheumatoid arthritis. *Hum Mol Genet* 1999; 8: 1707-13.
35. STEINKASSERER A, SPURR NK, COX S, JEGGO P, SIM RB: The human IL-1 receptor antagonist gene (IL1RN) maps to chromosome 2q14-q21, in the region of the IL-1a and IL-1b loci. *Genomics* 1992; 13: 654-7.
36. RAFIQ S, STEVENS K, HURST AJ *et al*.: Common genetic variation in the gene encoding interleukin-1-receptor antagonist (IL-1RA) is associated with altered circulating IL-1RA levels. *Genes Immnu* 2007: 8: 344-51.
37. CARTER MJ, JONES S, CAMP NJ *et al*.: Functional correlates of the interleukin-1 receptor antagonist gene polymorphism in the colonic mucosa in ulcerative colitis. *Genes Immun* 2004; 5: 8-15.
38. MALYAK M, SMITH MF JR, ABEL AA, HANCE KR, AREND WP: The differential production of three forms of IL-1 receptor antagonist by human neutrophils and monocytes. *J Immunol* 1998; 161: 2004-10.
39. REDLITZ KH, YAMSHCHIKOV VF, COMINELLI F: Differential contribution of IL-1Ra isoforms to allele-specific IL-1Ra mRNA accumulation. *J Interferon Cytokine Res* 2004; 24: 253-60.