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ORIGINAL RESEARCH

Usefulness of Cytokine Gene Polymorphisms for the Therapeutic Choice in Japanese Patients with Rheumatoid Arthritis

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Background: Rheumatoid arthritis (RA) is characterized by systemic synovitis with bone erosion and joint cartilage degradation. Although the analysis of polymorphisms in cytokine-encoding genes is important or understanding the pathophysiology of RA and selecting appropriate treatment for it, few studies have examined such single-nucleotide polymorphisms (SNPs) specifically in Japanese patients. This study was established to investigate the associations between polymorphisms in cytokine-encoding genes, autoantibodies and therapeutic responses in Japanese RA patients.

Methods: The subjects in this study consisted of 100 RA patients and 50 healthy controls. We extracted data on sex, age, disease duration, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, and therapeutic responses, including to methotrexate (MTX) and biological disease-modifying antirheumatic drugs (DMARDs). Genomic DNA was isolated from peripheral blood, which was genotyped for IL-10, TNF-α, TGF-β_1, and IFN-γ polymorphisms.

Results: Regarding IL-10 (−592 C/A and −819 C/T), significant decreases in the frequencies of the IL-10 (−592) CC genotype and (−819) CC genotype were found in RA patients compared with the levels in controls. For IFN-γ (+874 T/A), a significant decrease in the frequency of the TT genotype was found in RA patients compared with that in controls. Regarding TGF-β_1 (+869 T/C), patients with positivity for anti-CCP antibody had a significantly lower frequency of the CC genotype than those with negativity for it. Furthermore, the IL-10 (−592) CC genotype and (−819) CC genotype might be related to the biological DMARD-response.

Conclusion: Our results suggest that the analysis of polymorphisms in cytokine-encoding genes may be useful when selecting treatment for Japanese RA patients.

Keywords: RA, SNP, cytokine gene polymorphism, anti-CCP antibody, biological DMARD

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease, which afflicts 0.5–1% of the population worldwide.[1,2] Although an increasing number of reports have indicated that certain pathogens might be linked to RA, its exact cause remains unknown.[3–6] RA is characterized by systemic synovitis with bone erosion and joint cartilage degradation.[1] Specifically, osteoclast precursor cells in the inflamed synovium differentiate into osteoclasts in the presence of receptor activator of nuclear factor kappa-B ligand (RANKL) and inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), which directly affect bone

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destruction.[7] Therefore, cytokines play crucial roles in the pathogenesis of RA, making them targets for treating this disease. For this reason, biological disease-modifying antirheumatic drugs (DMARDs) such as TNF and IL-6 receptor inhibitors have become popular.[8]

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies are used for the diagnosis of RA.[9] RF is an antibody directed against the Fc region of IgG and is found in 70–90% of RA patients. It can also be found in patients with other autoimmune or infectious diseases, as well as healthy people.[10] In contrast, anti-CCP antibody is an antibody against arginyl residue peptide citrullinated by peptidylarginine deiminase; it is more specific to RA than RF.[9] Studies have also shown that patients positive for anti-CCP antibody are more prone to radiographic progression than those negative for it.[11,12] The production of autoantibodies is important for autoimmune diseases and cytokines play crucial roles in this process.[13]

The assumption that genetic factors are important in autoimmune diseases has led to extensive molecular studies being performed. The analysis of polymorphisms in cytokine-encoding genes is important or understanding the pathophysiology and establishing appropriate treatment.[14] The distribution of single-nucleotide polymorphisms (SNPs) varies among different ethnic groups, which is also the case specifically for polymorphisms in cytokine-encoding genes related to RA.[15,16] However, there have been few reports on cytokine-related polymorphisms in Japanese RA patients.[17] As such, this study was established to investigate the associations between polymorphisms in cytokine-encoding genes, autoantibodies, and therapeutic responses in Japanese RA patients.

Materials and Methods

Study Design and Subjects

This study was approved by the ethics committee of Kansai Medical University. All participants, or a parent or legal guardian for those under the age of 20 years, provided informed consent to participate in this study, which was conducted in accordance with the Declaration of Helsinki. The subjects in this study consisted of 100 RA patients and 50 healthy controls. The patients met the criteria for RA in the 1987 revised classification or the 2010 criteria. Therapeutic responses to MTX and biological DMARDs were determined using the DAS28 criteria after 6 months of therapy. Responders were defined as those having a DAS28 score <3.2 or an improvement in it of at least 1.2 points. Non-responders were defined as the rest. We extracted data on the patients' sex, age, disease duration, RF, anti-CCP antibody, and therapeutic responses, including to methotrexate (MTX) and biological DMARDs such as anti-TNF-α blockers and anti-IL-6 blockers.

Genotyping

Genomic DNA was isolated from ethylene diamine-tetraacetic acid (EDTA) whole peripheral blood using QIAamp DNA Mini Kit (Qiagen, Hilden, Germany). TNF-α, TGF-β_1, IL-10, and IFN-γ polymorphisms were analyzed the by polymerase chain reaction sequence-specific primer (PCR-SSP) method using Cytokine Genotyping Tray (One Lambda, Inc., Los Angeles, CA, USA). For TNF-α, the promoter region at position −308 G/A (rs1800629) was analyzed. For TGF-β_1, two polymorphisms in the coding region, namely, codon 10 +869 T/C (rs1982073) and codon 25 +915 C/G (rs1800471), were analyzed. For IL-10, three polymorphisms in the promoter region, namely, −1082 G/A (rs1800896), −819 C/T (rs1800871), and −592 C/A (rs1800872), were analyzed. Finally, for IFN-γ, the coding region position +874 T/A (rs2430561) was analyzed. DNA fragments corresponding to each cytokine were amplified in accordance with the manufacturer's instructions.

Statistical Analysis

Statistical analysis was performed using Fisher's exact test and Pearson's chi-squared test. The genotype distributions for the studied polymorphisms of the RA patients and control group individuals were statistically compared using Pearson's chi-squared test and Fisher's exact probability test with StatFlex v7 software. In addition, the genotype distribution was analyzed for the studied polymorphisms of two groups of RA patients divided by the presence or absence of anti-CCP antibody, as well as by whether treatment (with MTX and biological DMARD) had been undertaken. Results were considered statistically significant when the probability of findings occurring by chance was less than 5% ($P<0.05$). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for disease susceptibility, in groups with the presence or absence of anti-CCP antibody, and whether therapy such as MTX or biological DMARD had been undertaken.

Results

Patient Characteristics

The mean age of the RA patients was 61.1 ± 14.3 (range 17–85) years. A total of 85% of them were female. Data

on the medical history revealed the treatment modalities of the patients to be MTX (56 patients) and biological DMARDs (66 patients; TNF blocker 42 and IL-6 blocker 24). Baseline characteristics of the RA patients and healthy controls are given in Table 1. Anti-CCP antibody was detected in 70% of the RA patients. There were no differences between antibody-positive and -negative patients, in terms of sex, age, and disease duration (positive vs negative; proportion of females, 84.3% vs 86.7%; age, 59.8 ± 15.1 vs 64.1 ± 11.6; disease duration, 111.1 ± 111.4 vs 85.5 ± 85.2).

Association of Polymorphisms in Cytokine-Encoding Genes with RA Susceptibility

The findings showed significant decreases in the frequencies of the IL-10 (−592) CC genotype and (−819) CC genotype in RA patients compared with those in controls (8% vs 24%, χ^2=5.4162, p=0.01995, OR=0.333) (Table 2). Regarding IFN-γ (+874) a significant decrease in the frequency of the TT genotype was revealed in RA patients compared with that in controls (0% vs 6.0%, χ^2=5.7736, p=0.01627). However, no significant differences in TNF-α and TGF-β_1 genotypes were observed between the RA patients and controls.

Table 1 Baseline Characteristics of the RA Patients and Healthy Controls

	RA	Control
N	100	50
Age (years)	61.1±14.3	39.2±7.6
Age Range	17–85	26–61
Gender (F/M)	85/15	29/21
Disease duration (months)	103.4±104.9	—
Positive RF (%)	74 (74%)	—
Positive ACPA (%)	70 (70%)	—
The history of the treatment of RA (N)	MTX (56) Biological DMARD (66) TNF blocker (42) IL-6 blocker (24)	—
Complications (%)	Hypertension (22%) Lipid abnormalities (19%) Diabetes (12%) Hyperuricemia (11%) Heart diseases (5%) Autoimmune diseases (10%)	—

Abbreviations: RA, rheumatoid arthritis; RF, rheumatoid factor; ACPA, anti-cyclic citrullinated peptide antibody; MTX, methotrexate; DMARD, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor; IL-6, interleukin-6.

Association of Polymorphisms in Cytokine-Encoding Genes with Autoantibodies in RA Patients

Regarding TGF-β_1 (+869), patients with positivity for anti-CCP antibody had a significant decrease in the frequency of the CC genotype compared with those negative for it (20% vs 47%, χ^2=3.8788, p=0.04890, OR=0.429) (Table 3). No significant differences in IL-10, TNF-α, and IFN-γ genotype frequencies were observed between anti-CCP antibody-positive and -negative RA patients. Furthermore, no significant associations were found between RF and any polymorphism in cytokine-encoding genes (data not shown).

Association of Polymorphisms in Cytokine-Encoding Genes with Therapeutic Responses in RA Patients

MTX

A total of 56 patients with RA initiated MTX treatment at our hospital. Thirty-three of these responded to it, while 23 did not. There were no significant differences between responders and nonresponders to MTX treatment in RA patients (Table 4).

Biological DMARDs

A total of 66 patients were treated with biological DMARDs (anti-TNF blocker, 42 patients; anti-IL-6 blocker, 24 patients). Forty-eight of these responded to it, while 18 did not. The responders exhibited a significantly lower frequency of the IL-10-592 CC genotype and IL-10-819 CC genotype than the nonresponders (4% vs 20%, χ^2=4.0225, p=0.04490, OR=0.188) (Table 5).

Discussion

IL-10 is an anti-inflammatory cytokine mainly produced by Th2 cells and a variety of other cells, such as helper T (Th)1 cells, Th17 cells, B cells and macrophages.[18] This cytokine suppresses the secretion of Th1 cytokines, deactivates macrophages and natural killer cells, and is also involved in the differentiation of B cells and antibody production.[19] In the serum and synovial fluid of RA patients, IL-10 levels

Table 2 Frequencies of Cytokine Gene Polymorphisms in RA and Normal Controls

Polymorphism	Genotype	100 Patients N (%)	50 Controls N (%)	χ^2 value	P value	OR	95% CI
TNF-α-308	G/G	99 (99)	50 (100)	0.0017	0.96730	0.990	0.612–1.601
	A/A	0 (0)	0 (0)	—	—	—	—
	G/A	1 (10)	0 (0)	0.4983	0.48023	—	—
TGF-β_1 +869	T/T	20 (20)	13 (26)	0.4401	0.50707	0.769	0.354–1.672
	C/C	28 (28)	11 (22)	0.3724	0.54170	1.273	0.586–2.764
	T/C	52 (52)	26 (52)	—	—	—	—
TGF-β_1 +915	C/C	0 (0)	0(0)	—	—	—	—
	G/G	100 (100)	50 (100)	—	—	—	—
	C/G	0 (0)	0(0)	—	—	—	—
IL-10-592	C/C	**8 (8)**	**12 (24)**	**5.4162**	**0.01995**	**0.333**	**0.128–0.868**
	A/A	46 (46)	20 (40)	0.1921	0.66114	1.150	0.615–2.149
	C/A	46 (46)	18 (36)	0.5613	0.45372	1.278	0.672–2.428
IL-10-819	C/C	**8 (8)**	**12 (24)**	**5.4162**	**0.01995**	**0.333**	**0.128–0.868**
	T/T	46 (46)	20 (40)	0.1921	0.66114	1.150	0.615–2.149
	C/T	46 (46)	18 (36)	0.5613	0.45372	1.278	0.672–2.428
IL-10-1082	G/G	0 (0)	0 (0)	—	—	—	—
	A/A	94 (94)	47 (94)	—	—	—	—
	G/A	6 (6)	3 (6)	—	—	—	—
IFN-γ +874	T/T	**0 (0)**	**3 (6)**	**5.7736**	**0.01627**	—	—
	A/A	79 (49)	39 (78)	0.0024	0.96112	1.013	0.607–1.690
	T/A	21 (21)	8 (16)	0.3665	0.54494	1.313	0.543–3.171

Note: Bold numbers are statistically significant ($p < 0.05$).
Abbreviations: N, absolute number; OR, odds ratio; CI, confidence interval; TNF, tumor necrosis factor; TGF, transforming growth factor; IL-10, interleukin-10; IFN, interferon.

are elevated compared with those in healthy people.[20] Furthermore, it has been reported that IL-10 suppress joint swelling and deformation in an RA animal model.[21,22] Therefore, IL-10 may be involved in the pathophysiology of RA. In this study, regarding IL-10 (−819 C/T and −592 C/A), significant decreases in the frequencies of the IL-10 (−592) CC genotype and (−819) CC genotype were found in RA patients compared with those in controls. Several studies have reported an association between IL-10 polymorphism and susceptibility to RA.[23,24] Similar to these previous reports, our results indicated that IL-10 is strongly involved in the pathophysiology of RA.

IFN-γ is produced by Th1 and Th2 cells, and IFN-γ and IL-4 inhibit differentiation into osteoclasts.[25] IFN-γ is decreased in the synovium of RA patients, which leads to deterioration of the suppression of osteoclastogenesis and affects bone destruction.[26] In our study, there was a significant decrease in the frequency of the TT genotype of the IFN-γ (+874 A/T) polymorphisms in RA patients compared with that in controls. This suggests the possibility that IFN-γ polymorphism is involved in the pathophysiology of RA. Khani-Hanjani et al[27] reported the associations of IFN-γ (+874 A/T) polymorphism with susceptibility to, and severity of, RA. However, other studies have reported that IFN-γ polymorphisms are not associated with the susceptibility to RA.[28–30] In addition, a recent meta-analysis by Lee et al[31] indicated that the IFN-γ (+874 A/T) polymorphism may play a significant role in modifying the risk of autoimmune diseases in Caucasian, Latin American, and Middle Eastern subjects, and in particular showed that this polymorphism is associated with increased susceptibility to idiopathic thrombocytopenic purpura and systemic lupus erythematosus (SLE). Furthermore, Teker et al[32] demonstrated that T/T genotype of the IFN-γ (+874 A/T) polymorphism is associated with both rheumatic heart disease and the severity of this disease. Similarly, the association between IFN-γ (+874 A/T) polymorphism and RA seems to be controversial. Therefore, our results concerning IFN-γ might be valid only in Japanese patients.

Table 3 Distribution of Cytokine Genotypes in ACPA-Positive and -Negative Patients with RA

Polymorphism	Genotype	ACPA-(+) 70 Patients N (%)	ACPA-(−) 30 Patients N (%)	χ^2 value	P value	OR	95% CI
TNF-α-308	G/G A/A G/A	70 (100) 0 (0) 0 (0)	29 (97) 0 (0) 1 (3)	0.0119 — 2.2806	0.91305 — 0.13100	1.034 — —	0.563–1.901 — —
TGF-β_1 +869	T/T C/C T/C	14 (20) **14 (20)** 42 (60)	6 (20) **14 (47)** 10 (33)	— **3.8788** 2.0462	— **0.04890** 0.15259	— **0.429** 1.800	— **0.182–1.008** 0.800–4.052
TGF-β_1 +915	C/C G/G C/G	0 (0) 70 (100) 0 (0)	0(0) 30 (100) 0(0)	— — —	— — —	— — —	— — —
IL-10-592	C/C A/A C/A	7 (10) 30 (43) 33 (47)	1 (3) 16 (53) 13 (43)	1.1085 0.3340 0.0459	0.29241 0.56334 0.83042	3.000 0.804 1.088	0.353–25.460 0.382–1.688 0.503–2.353
IL-10-819	C/C T/T C/T	7 (10) 30 (43) 33 (47)	1 (3) 16 (53) 13 (43)	1.1085 0.3340 0.0459	0.29241 0.56334 0.83042	3.000 0.804 1.088	0.353–25.460 0.382–1.688 0.503–2.353
IL-10-1082	G/G A/A G/A	0 (0) 64 (91) 6 (9)	0 (0) 30 (100) 0 (0)	— 0.0832 2.5105	— 0.77305 0.11309	— 0.914 —	— 0.194–1.681 —
IFN-γ +874	T/T A/A T/A	0 (0) 56 (80) 14 (20)	0 (0) 23 (77) 7 (23)	— 0.0166 0.0908	— 0.89741 0.76311	— 1.043 0.857	— 0.546–1.993 0.314–2.337

Note: Bold numbers are statistically significant ($p < 0.05$).
Abbreviations: ACPA-(+), anti-cyclic citrullinated peptide antibody-positive; ACPA-(−), anti-cyclic citrullinated peptide antibody-negative; other abbreviations, see Table 2.

In the present study, we also investigated the association of polymorphisms in cytokine-encoding genes with autoantibodies in RA patients. Interestingly, regarding TGF-β_1 (+869 T/C), we found that patients with positivity for anti-CCP antibody had a significantly lower frequency of the CC genotype than patients negative for it. TGF-β_1 is produced by T cells, dendritic cells and macrophages, and plays essential roles in regulating immune function and controlling cell growth and differentiation.[33] Serum TGF-β_1 level is elevated in diseases associated with fibrosis, while it is decreased in SLE.[34–36] Moreover, TGF-β_1-deficient mice have been shown to exhibit enhanced autoantibody production and inflammatory cell infiltration. This could be related to the pathology of SLE,[37] although TGF-β_1 levels were reported not to differ significantly between RA patients and healthy controls.[38] Therefore, TGF-β_1 can participate in the production of autoantibodies in RA patients. Actually, it was reported that the TGF-β_1 (+869) T allele was significantly associated with RA in Asians,[38] which is consistent with our results. Additionally, Alayli et al[39] reported that Turkish RA patients with the TGF-β_1 (+869) T allele may have an increased risk of RF positivity, although little has been reported on anti-CCP antibody and TGF-β_1 polymorphisms. As we mentioned earlier, TGF-β_1 is produced by T cells, dendritic cells, and macrophages, and plays essential roles in regulating immune function and controlling cell growth and differentiation.[33] Given that patients positive for anti-CCP antibody are more prone to radiographic progression than those negative for it, we may be able to use TGF-β_1 polymorphism as a predictor of radiographic progression. However, there is a need for further investigation of the feasibility of this.

Several studies have reported that polymorphisms in cytokine-encoding genes are associated with therapeutic responses in RA patients.[40–43] In the present study, we investigated the relationship between such polymorphisms and the therapeutic responses to MTX and biological DMARDs in RA patients. There were no significant

Table 4 Distribution of Cytokine Genotypes in MTX-Responder and -Nonresponder Patients with RA

Polymorphism	Genotype	MTX-Res. 33 Patients N (%)	MTX-Non. 23 Patients N (%)	χ^2 value	P value	OR	95% CI
TNF-α-308	G/G A/A G/A	33 (100) 0 (0) 0 (0)	23 (100) 0 (0) 0 (0)	— — —	— — —	— — —	— — —
TGF-β_1 +869	T/T C/C T/C	6 (18) 9 (27) 18 (55)	7 (30) 6 (26) 10 (44)	0.7006 0.0056 0.2246	0.40257 0.94024 0.63556	0.597 1.045 1.255	0.178–2.010 0.327–3.342 0.491–3.207
TGF-β_1 +915	C/C G/G C/G	0 (0) 33 (100) 0 (0)	0(0) 23 (100) 0(0)	— — —	— — —	— — —	— — —
IL-10-592	C/C A/A C/A	1 (3) 15 (45) 17 (52)	2 (8) 10 (44) 11 (48)	0.7639 0.0082 0.0247	0.38210 0.92777 0.87510	0.348 1.045 1.077	0.030–4.074 0.400–2.733 0.426–2.721
IL-10-819	C/C T/T C/T	1 (3) 15 (45) 17 (52)	2 (8) 10 (44) 11 (48)	0.7639 0.0082 0.0247	0.38210 0.92777 0.87510	0.348 1.045 1.077	0.030–4.074 0.400–2.733 0.426–2.721
IL-10-1082	G/G A/A G/A	0 (0) 30 (91) 3 (9)	0 (0) 22 (96) 1 (4)	— 0.0170 0.4018	— 0.89640 0.52617	— 0.950 2.091	— 0.442–2.044 0.204–21.382
IFN-γ +874	T/T A/A T/A	0 (0) 29 (88) 4 (12)	0 (0) 21 (91) 2 (9)	— 0.0094 0.1349	— 0.92284 0.71345	— 0.962 1.394	— 0.444–2.084 0.235–8.257

Abbreviations: MTX-res, methotrexate-responder; MTX-non, methotrexate-nonresponder; other abbreviations, see Table 2.

differences between responders and nonresponders to MTX treatment in RA patients. Furthermore, those who responded to biological DMARDs exhibited a significantly lower frequency of the IL-10 (-592) CC genotype and IL-10 (-819) CC genotype than those who did not. Other reports also described the existence of a relationship between TNF-α −308 G/A and anti-TNF -α blocker.[40–42] However, our results did not show such relationships. It was previously reported that the effect of anti-TNF blocker may be related to polymorphisms in cytokine-encoding genes other than TNF-α.[44] The mechanisms behind the differences in therapeutic responses depending on such polymorphisms remain incompletely understood.[45] One factor o influencing this could be ethnic differences. Further studies are needed to clarify the association between polymorphisms in cytokine-encoding gene and therapeutic responses.

This study had some limitations. First, the sample size of this study was too small to draw any robust conclusions. Second, the samples were probably not representative of the Japanese RA population, because data were obtained from only a single facility. Finally, we did not completely define the relationship between polymorphisms in cytokine-encoding genes and biological DMARDs other than anti-TNF and -IL-6 blockers in this study. Therefore, it remains unknown whether all biological DMARDs in RA patients are directly linked to such polymorphisms. Future prospective studies will be needed to confirm the observations from this study.

Conclusions

This study showed that the IL-10 (−592 CC, −819 CC) and IFN-γ (+874 TT) genotypes might be related to RA in the Japanese. Additionally, the TGF-β_1 (+869 CC) genotype may be associated with the production of anti-CCP antibody. Furthermore, the IL-10 (−592 CC, −819 CC) genotype might be linked to the biological DMARD response. These results suggest that analyzing polymorphisms in cytokine-encoding genes could be useful when selecting treatment for Japanese RA patients.

Table 5 Distribution of Cytokine Genotypes in BDM-Responder and -Nonresponder Patients with RA

Polymorphism	Genotype	BDM.-Res. 48 Patients N (%)	BDM.-Non. 18 Patients N (%)	χ^2 value	P value	OR	95% CI
TNF-α-308	G/G A/A G/A	48 (100) 0 (0) 0 (0)	18 (100) 0 (0) 0 (0)	— — —	— — —	— — —	— — —
TGF-β_1 +869	T/T C/C T/C	11 (23) 9 (19) 28 (58)	5 (28) 3 (17) 10 (55)	0.1009 0.0267 0.0112	0.75070 0.87030 0.91563	0.825 1.125 1.050	0.252–2.706 0.273–4.629 0.426–2.589
TGF-β_1 +915	C/C G/G C/G	0 (0) 48 (100) 0 (0)	0(0) 18 (100) 0(0)	— — —	— — —	— — —	— — —
IL-10-592	C/C A/A C/A	**2 (4)** 25 (52) 21 (44)	**4 (22)** 6 (33) 8 (45)	**4.0225** 0.7102 0.0010	**0.04490** 0.39939 0.97482	**0.188** 1.563 0.984	**0.032–1.114** 0.551–4.433 0.370–2.618
IL-10-819	C/C T/T C/T	**2 (4)** 25 (52) 21 (44)	**4 (22)** 6 (33) 8 (45)	**4.0225** 0.7102 0.0010	**0.04490** 0.39939 0.97482	**0.188** 1.563 0.984	**0.032–1.114** 0.551–4.433 0.370–2.618
IL-10-1082	G/G A/A G/A	0 (0) 43 (90) 5 (10)	0 (0) 15 (83) 3 (17)	— 0.0315 0.3672	— 0.85923 0.54454	— 1.075 0.625	— 0.483–2.391 0.135–2.888
IFN-γ +874	T/T A/A T/A	0 (0) 35 (73) 13 (27)	0 (0) 15 (83) 3 (17)	— 0.1040 0.4910	— 0.74714 0.48348	— 0.875 1.625	— 0.388–1.971 0.414–6.378

Note: Bold numbers are statistically significant ($p < 0.05$).

Abbreviations: BDM-res, biological disease-modifying antirheumatic drug-responder; BDM-non, biological disease-modifying antirheumatic drug-nonresponder; other abbreviations, see Table 2.

Abbreviations

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; DMARD, disease-modifying antirheumatic drugs; RF, rheumatoid factor; CCP, cyclic citrullinated peptide; TNF, tumor necrosis factor; IFN, interferon; TGF, transforming growth factor; IL-10, interleukin-10; SNP, single-nucleotide polymorphism; MTX, methotrexate; PCR-SSP, polymerase chain reaction sequence-specific primer; OR, odds ratio; CI, confidence interval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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