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RESEARCH ARTICLE

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Association between C-reactive protein gene variant and treatment efficacy of etanercept in ankylosing spondylitis patients receiving hip arthroplasty

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Abstract

Background: C-reactive protein (CRP) level is one of the most widely used parameters to assess ankylosing spondylitis (AS), since CRP is associated with poor radiographic progression of AS patients. Recent studies have investigated the association between CRP gene variants and AS risk, but with conflicting findings.

Material and Methods: We enrolled 232 AS cases and 314 controls in this case-control study. Next, we assessed the association of CRP gene rs3091244 polymorphism with the efficacy of etanercept for AS. Genotyping was done using a custom-by-design 48-Plex SNP scanTM Kit.

Results: CRP gene rs3091244 polymorphism was associated with an increased risk of AS in this Chinese population. Clinical indicators of AS patients including morning stiffness time, Bath AS function index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Visual Analogue Scale (VAS), erythrocyte sedimentation rate (ESR), and CRP were significantly decreased after 12 weeks of etanercept treatment. Furthermore, AA genotype carriers showed higher values of VAS, BASDAI, BASFI, and CRP before etanercept treatment. AA genotype or A allele of rs3091244 polymorphism was associated with Ankylosing Spondylitis Assessment Study group response criteria 20 scores (ASAS20) and Assessment in SpondyloArthritis international Society 40 response (ASAS40) improvement. In addition, AA genotype carriers showed significantly higher CRP levels compared with genotype GG carriers (16.3 vs 8.8 mg/L).

Conclusion: CRP gene rs3091244 polymorphism is associated with an increased risk of AS. Additionally, rs3091244 polymorphism could serve as a biomarker for good response to etanercept treatment in AS.

KEYWORDS

ankylosing spondylitis, case-control study, C-reactive protein, etanercept

Abbreviations: AS, ankylosing spondylitis; ASAS20, Ankylosing Spondylitis Assessment Study group response criteria 20 scores; ASAS40, Assessment in SpondyloArthritis international Society 40 response; BASDAI, Bath AS activity index; BASFI, Bath AS function index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SNP, single nucleotide polymorphism; VAS, Visual Analogue Scale.

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1 | INTRODUCTION

Ankylosing spondylitis (AS), a chronic inflammatory disorder, causes ossification of sacroiliac joints and axial skeleton and thereby affects sacroiliac joints, spine, and other tissues.[1] Up to date, the etiology of AS remains poorly understood. Emerging evidence shows that genetic, immunological, and environmental factors contribute to AS development.[2] Among genetic factors, human leukocyte antigen B27 (HLA-B27) gene is frequently positive in AS patients,[3] but not all AS patients carry HLA-B27 gene, suggesting that other genetic factors may also affect the susceptibility to AS.[4-6]

C-reactive protein (CRP), an inflammatory cytokine and one acute-phase protein, has been extensively studied in AS. HLA-B27-positive AS patients usually have higher CRP levels than HLA-B27-negative AS patients.[7] CRP has a short half-life, and its level rises rapidly during inflammation. CRP levels affect the severity, clinical progression, and treatment response of AS.[8-10] Hence, CRP is the most useful marker of clinical remission with AS treatment. CRP is also related to poor radiographic progression in AS patients.[11,12] CRP gene is located in the 1q23.2 region near the long arm of chromosome 1. Many factors (eg, age, gender, smoking habits, and body mass index) could affect the baseline level of serum CRP.[9] However, single nucleotide polymorphisms (SNPs) in the CRP gene also affect CRP levels.[13,14] Furthermore, CRP levels are associated with different CRP alleles and haploids.[15]

CRP gene rs3091244 polymorphism, a SNP in the exon region, may influence the RNA translation, stability, and transcription and then alter the CRP protein expression. Although CRP levels are affected in many ways, single nucleotide gene mutations also significantly impact serum CRP levels.[16] Etanercept, a tumor necrosis factor alpha (TNF-α) inhibitor, is effective in AS treatment.[17] Both baseline and post-baseline CRP levels could significantly predict treatment with TNF-a blocker in AS patients.[18] SNP maps are pivotal in identifying individual differences in response to pharmacogenomics drugs. However, whether CRP gene rs3091244 polymorphism affects the therapeutic effect of etanercept in AS patients is unsolved. In addition, the association between CRP gene rs3091244 polymorphism and AS risk was explored in Caucasian populations,[19,20] but no Chinese studies addressed this issue. For the above reasons, we designed this case-control study to assess the association between CRP gene rs3091244 polymorphism and AS risk, and the efficacy of etanercept treatment for AS patients in a Chinese Han population.

2 | PATIENTS AND METHODS

2.1 | Subjects

In this case-control study, 232 HLA-B27-positive AS patients and 314 sex- and age-matched controls were recruited from Changzhou Second Affiliated Hospital of Nanjing Medical University (Changzhou, China), Changzhou First Hospital (Changzhou, China), and Jinling Hospital (Nanjing, China). The diagnosis of all AS patients met with the 1984 revised New York Criteria of the American College of Rheumatology.[21] Inclusion criteria were (a) diagnosis of AS according to the New York Criteria of the American College of Rheumatology; (b) no use of corticosteroids or other immunosuppressive drugs; (c) with normal hepatic and renal function; (d) reception of hip arthroplasty; and (e) good response to etanercept. Exclusion criteria were (a) patients receiving hormone therapy in 3 months before the recruitment; (b) peptic ulcer, diabetes, chronic obstructive pneumonia, chronic nephritis, or other autoimmune diseases; and (c) other thromboembolic diseases. The control individuals received health examinations in the same hospitals at the same period.

The study was approved by the Ethics Committees of the three studied Hospitals. This study met the standards of Declaration of Helsinki. All participants provided written informed consent to participate in this study.

2.2 | Blood sampling and genotyping

DNA samples of all individuals from peripheral leukocytes were isolated using a TIANamp Blood DNA Kit according to the manufacturer's instructions (Qiagen). Blood plasma CRP levels in the 231 AS patients were tested using an enzyme-linked immunosorbent assay kit (Boster). The CRP levels were calculated by referring to a standard curve according to the manufacturer's instructions. CRP gene rs3091244 polymorphism was genotyped using a custom-by-design 48-Plex SNP scanTM Kit (Genesky Biotechnologies Inc) with the following primers: ATTTCCCAGTCTGTAAATAAG CAAA (forward) and AATGGGAAATGGTAACATATTAATC (reverse). About 10% of selected samples were re-genotyped to verify the genotyping accuracy. The concordance of genotypes in the repeated samples was 100%.

2.3 | Statistical analysis

Differences in frequency distributions of dichotomous variables between cases and controls were evaluated using the chi-square test. Categorical variables and continuous variables are shown as percentages and mean ± standard deviation (SD), respectively. The Hardy-Weinberg equilibrium (HWE) for CRP gene rs3091244 polymorphism was assessed among the controls. Logistic regression was used to evaluate the relationship between this polymorphism and AS risk. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated without or with adjustment for both age and sex. The association between CRP gene rs3091244 polymorphism and therapeutic effect of etanercept was investigated. $P < .05$ was considered statistically significant. Differences in CRP gene polymorphism and CRP levels were evaluated using Student's *t* test. All data were analyzed using SPSS 22.0 (SPSS Inc).

2.4 | Power analysis

The comprehensive statistical power of this study was analyzed using Genetic Power Calculator 33 at the significant value of .05.

3 | RESULTS

3.1 | Characteristics of the study population

Table 1 summarizes the demographic data of 232 AS patients and 314 healthy controls recruited in this case-control study. No significant differences between case and control groups were found in the distribution of age, sex, height, weight, or body mass index (BMI).

3.2 | Association between CRP gene rs3091244 polymorphism and AS risk

CRP gene rs3091244 polymorphism in the control group met with HWE ($P > .05$). Moreover, the AA or AA+GA genotype was associated with an increased risk of AS (AA vs GG: OR, 1.94; 95% CI, 1.06-3.57; $P = .033$; AA+GA vs GG: OR, 1.47; 95% CI, 1.05-2.07; $P = .027$). After adjustment of sex and age, these associations still held true (Table 2). In addition, A allele was also related to an increased risk of AS (AA vs GG: OR, 1.39; 95% CI, 1.07-1.81; $P = .013$). Power analysis showed this study had a power of 86.3% in detecting the association between CRP rs3091244 polymorphism and AS risk (OR = 1.47).

3.3 | Therapeutic effect of etanercept on AS patients

Next, we explored the therapeutic effect of etanercept on AS patients. The clinical indicators of AS patients including morning stiffness time, Bath AS function index (BASFI), Bath AS activity index (BASDAI), Visual Analogue Scale (VAS), erythrocyte sedimentation rate (ESR), and CRP were all significantly decreased after 12 weeks of etanercept treatment ($P < .05$; Table 3), indicating the good therapeutic effect of etanercept on AS patients.

TABLE 1 Baseline characteristics of AS patients and controls

Parameters	AS	Control	*P*
N	232	314	
Age, years	62.35 ± 8.21	62.02 ± 7.83	.634
Weight, kg	54.98 ± 9.52	55.65 ± 9.01	.401
Height, cm	165.52 ± 16.13	164.28 ± 17.84	.404
BMI, kg/m^2	20.73 ± 5.79	21.34 ± 5.80	.221
Male/Female	122/110	156/158	.502

Abbreviation: BMI, body mass index.

3.4 | Association between CRP gene rs3091244 polymorphism and clinical indicators of AS before and after etanercept treatment

Before etanercept treatment, AA genotype carriers showed higher values of VAS, BASDAI, BASFI, and CRP (Table 4). After 12 weeks of etanercept treatment, all these four indicators significantly decreased in all AS patients. However, AA genotype carriers still showed high values of BASDAI, BASFI, CRP compared with GA or GG genotype carriers.

3.5 | Association of CRP gene rs3091244 polymorphism with the efficacy of etanercept for AS

Ankylosing Spondylitis Assessment Study group response criteria 20 scores (ASAS20) and Assessment in SpondyloArthritis international Society 40 response (ASAS40) were used to detect the relationship between CRP gene rs3091244 polymorphism and etanercept treatment. After 12 weeks of etanercept treatments, AA genotype or A allele showed a positive impact on the rate of ASAS20 and ASAS40 improvement (Table 5).

3.6 | Association of CRP gene rs3091244 polymorphism with the serum CRP levels in AS patients

Last, we explored whether different genotypes of CRP gene rs3091244 polymorphism were associated with CRP levels. Data showed that AA genotype carriers showed significantly higher CRP levels compared with genotype GG carriers (16.3 vs 8.8 mg/L) (Table 6). However, no significant difference about CRP levels was found between GA and GG genotype carriers in AS patients.

4 | DISCUSSION

This case-control study found that CRP gene rs3091244 polymorphism was associated with an increased risk of AS in this tested Chinese population. Morning stiffness time, BASFI, BASDAI, VAS, ESR, and CRP all significantly decreased after 12 weeks of etanercept treatment. Furthermore, AA genotype carriers showed higher values of VAS, BASDAI, BASFI, and CRP before etanercept treatment. AA genotype or A allele of rs3091244 polymorphism was associated with ASAS20 and ASAS40 improvement. Meanwhile, AA genotype carriers showed significantly higher CRP level compared with genotype GG carriers.

Current therapeutic ways for AS patients are limited. In fact, an increasing number of AS patients have been successfully treated with anti-TNF therapies. The TNF-α inhibitor etanercept is reportedly effective in AS treatment.[22] Etanercept consists of a recombinant human TNF receptor, which can block the cytokine

TABLE 2 Genotype frequencies of CRP gene polymorphism in AS cases and controls

Models	Genotype	Case (n, %)	Control (n, %)	OR (95% CI)	*P*-value	[a]OR (95% CI)	[a]*P*-value
Co-dominant	GG	101 (43.7%)	167 (53.4%)	1.00 (reference)	—	1.00 (reference)	—
Heterozygote	GA	103 (44.6%)	123 (39.3%)	1.39 (0.97-1.98)	.076	1.41 (0.98-2.03)	.064
Homozygote	AA	27 (11.7%)	23 (7.3%)	**1.94 (1.06-3.57)**	**.033**	**1.98 (1.08-3.65)**	**.028**
Dominant	GG	101 (43.7%)	167 (53.4%)	1.00 (reference)	—	1.00 (reference)	—
	AA+GA	130 (56.3%)	146 (46.6%)	**1.47 (1.05-2.07)**	**.027**	**1.50 (1.06-2.12)**	**.021**
Recessive	GA+GG	204 (88.3%)	290 (92.7%)	1.00 (reference)	—	1.00 (reference)	—
	AA	27 (11.7%)	23 (7.3%)	1.67 (0.93-2.99)	.086	1.68 (0.94-3.02)	.081
Allele	G	305 (66.0%)	457 (73.0%)	1.00 (reference)	—	1.00 (reference)	—
	A	157 (34.0%)	169 (27.0%)	**1.39 (1.07-1.81)**	**.013**	**—**	**—**

Note: The genotyping was successful in 231 cases and 313 controls;
Bold values are statistically significant ($P < .05$).
[a]Adjust age and sex.

TABLE 3 The six clinical parameters of AS patients before and after etanercept treatment

Group	Time	Morning stiffness time(min)	VAS	BASDAI	BASFI	ESR (mm/h)	CRP (mg/L)
Etanercept	0 wk	32.24 ± 9.95	5.91 ± 2.00	56.40 ± 25.42	56.53 ± 24.49	49.84 ± 18.01	44.29 ± 14.90
	12 wk	12.20 ± 4.85[a]	2.07 ± 0.79[a]	17.08 ± 10.43[a]	16.87 ± 24.34[a]	20.92 ± 6.99[a]	15.05 ± 4.45[a]
	Difference	20.03 ± 11.50	3.84 ± 2.12	39.32 ± 26.50	39.66 ± 25.58	28.92 ± 19.41	29.24 ± 15.62

Abbreviations: BASDAL, Bath ankylosing spondylitis disease activity index; BASFL, Bath ankylosing spondylitis function index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; VAS, Visual Analog Scale.
[a]Comparison between pre- and pro-treatment showed significant difference ($P < .05$).

TABLE 4 The association between CRP gene rs3091244 polymorphism and clinical indicators of AS patients before and after etanercept treatment

		Groups				
Parameters	Time (wk)	GG	GA	AA	P1	P2
Morning stiffness time(min)	0	32.13 ± 10.17	32.18 ± 9.92	33.36 ± 9.35	0.972	0.570
	12	12.07 ± 5.06	12.15 ± 4.83	12.78 ± 4.20	0.912	0.505
VAS	0	5.84 ± 1.93	5.81 ± 2.02	6.70 ± 2.04	0.897	**0.044**
	12	2.04 ± 0.80	2.14 ± 0.76	1.93 ± 0.87	0.377	0.521
BASDAI	0	53.94 ± 25.89	55.24 ± 26.01	69.85 ± 17.14	0.722	**0.003**
	12	15.76 ± 9.99	17.44 ± 11.50	20.46 ± 6.70	0.269	**0.023**
BASFI	0	57.82 ± 26.11	51.95 ± 23.87	68.99 ± 12.41	0.095	**0.033**
	12	16.01 ± 9.56	17.07 ± 7.86	19.83 ± 5.16	0.390	**0.048**
ESR (mm/h)	0	50.92 ± 17.00	48.44 ± 19.15	50.76 ± 17.69	0.330	0.966
	12	22.03 ± 6.52	20.28 ± 7.04	19.94 ± 7.46	0.067	0.154
CRP (mg/L)	0	43.12 ± 15.75	43.53 ± 15.02	51.90 ± 7.85	0.851	**0.006**
	12	14.76 ± 4.79	14.67 ± 4.32	17.89 ± 1.52	0.882	**0.001**

Bold values are statistically significant ($p < .05$). Abbreviations: AA, adenine/adenine; BASDAL, Bath ankylosing spondylitis disease activity index; BASFL, Bath ankylosing spondylitis function index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GA, guanine/adenine; GG, guanine/guanine; P1, GA vs GG; P2, AA vs GG; VAS, Visual Analog Scale.

TNF-α and decrease chronic inflammation.[23] The use of etanercept is 50 mg once a week or 25 mg/d twice a week subcutaneously.[24] As reported, all clinical and laboratory measures of AS activity were reduced after etanercept treatment.[25,26] BASDAI scores of most AS patients were improved after etanercept therapy.[27] ESR and CRP levels are the most widely used parameters to assess

TABLE 5 Association of gene polymorphism of CRP with the efficacy of etanercept treatment for AS

Gene	SNP		Sample size(n)	ASAS20 effects				ASAS40 effects			
				Yes (n)	No (n)	OR (95% CI)	*P*	Yes (n)	No (n)	OR (95% CI)	*P*
CRP											
	Genotype	GG	101	88	13	1.00 (reference)	—	76	25	1.00 (reference)	—
		GA	103	86	17	1.34 (0.61-2.92)	.456	68	35	1.57 (0.85-2.88)	.149
		AA	27	18	9	**3.39 (1.26-9.11)**	**.016**	15	12	**2.43 (1.01-5.88)**	**.049**
	Allele	G	305	262	43	1.00 (reference)	—	220	85	1.00 (reference)	—
		A	157	122	35	**1.75 (1.07-2.87)**	**.027**	95	59	**1.61 (1.07-2.42)**	**.023**

Bold values are statistically significant ($P < .05$).

TABLE 6 Mean serum CRP values (mg/L) for different genotypes of CRP gene rs3091244 polymorphism

Genotypes	N (frequency)	Mean CRP (mg/L)	*P*-value
rs3091244 G>A			
GG	101 (43.7%)	8.8	ref
GA	103 (44.6%)	9.1	.36
AA	27 (11.7%)	16.3	**.00**

Note: Mean serum CRP levels for CRP gene rs3091244. Bold values are statistically significant ($P < .05$).

AS.[28] CRP is related to poor radiographic progression of AS patients.[12] Moreover, SNPs of some genes could predict treatment response to etanercept in AS patients.[29-31] Thus, we assumed that CRP gene rs3091244 polymorphism may affect the efficacy of etanercept for AS patients. Firstly, we found that etanercept could decrease the morning stiffness time, BASFI, BASDAI, VAS, ESR, and CRP. Secondly, AA genotype carriers showed higher values of VAS, BASDAI, BASFI, and CRP before etanercept treatment. Next, we evaluated the relationship between ASAS20 or ASAS40 and CRP gene rs3091244 polymorphism after etanercept treatment and observed that the AA genotype or A allele of this SNP positively impacted the rate of ASAS20 and ASAS40 improvement, indicating a role of rs3091244 polymorphism in the therapeutic effects of etanercept on AS patients. To our knowledge, this is first study to investigate the association between CRP gene rs3091244 polymorphism and therapeutic effects of etanercept in AS patients. The reasons why CRP gene rs3091244 polymorphism was associated with the response to etanercept treatment are unclear. Reportedly, both baseline and post-baseline CRP levels could significantly predict treatment with TNF-a blocker in AS patients.[18] This study showed AA genotype carriers showed significantly higher CRP levels compared with genotype GG carriers. Thus, we assume that rs3091244 polymorphism affects the CRP levels, thereby exerting effects on the etanercept treatment. However, further studies should be conducted to validate this assumption.

Recently, two Caucasian studies have addressed the association between CRP gene rs3091244 polymorphism and AS risk[19,20] and both showed that CRP gene rs3091244 polymorphism was associated with an increased risk of AS, which was in line with our findings. This present study demonstrated that AA+GA or AA genotype was associated with an increased risk of AS. Additionally, A allele was associated with a higher risk of AS. Nevertheless, further studies in other races are urgently needed to validate these findings.

Several limitations of this study should be noted. First, the sample size is small. Second, other functional SNPs should also be explored. Third, other factors associated with etanercept treatment in AS patients have not been assessed. Fourth, the underlying mechanism why CRP gene rs3091244 polymorphism affects etanercept treatment should be studied. Last, etanercept dosage should be studied in AS patients with different genotypes.

In conclusion, CRP gene rs3091244 polymorphism is associated with an increased risk of AS, and this SNP may serve as a biomarker for response to etanercept treatment in AS patients. These findings could help clinicians to offer patients more reasonable and specific prescription according to different genetic backgrounds.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, YX; Methodology, YX and WJ; Validation, HZ; Formal Analysis, YX; Investigation, HZ; Resources, HZ; Data Curation YX; Writing-Original Draft Preparation, WJ; Writing-Review and Editing, WJ and HZ.

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