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Original Article

Association of HSP90B1 genetic polymorphisms with efficacy of glucocorticoids and improvement of HRQoL in systemic lupus erythematosus patients from Anhui Province

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Abstract: *Objective:* The aim of this study was to investigate the associations between HSP90B1 gene polymorphisms and the efficacy of glucocorticoids (GCs) and the improvement of health-related quality of life (HRQoL) in Anhui patients with systemic lupus erythematosus (SLE). *Method:* A total of 305 patients with SLE were recruited to the study. These patients were treated with GCs for 12 weeks and classified into two groups (sensitivity and insensitivity) according to the response to GCs measured by the scores on SLE disease activity index (SLEDAI). The HRQoL of SLE patients were evaluated by 36-item Short Form Health Survey (SF-36) at baseline and 12 weeks respectively. HapMap database and Haploview software were used to select HSP90B1 gene tag single nucleotide polymorphisms (SNPs). Benjamini & Hochberg (BH) method based on false discovery rate (FDR) was used for multiple testing correction. *Results:* A total of 291 patients were included in final data analysis with 14 patients excluded due to loss to follow-up. Among these patients, 160 patients were sensitive to GCs and 131 patients were insensitive to GCs. Twelve tag SNPs of HSP90B1 gene were selected. The rs12426382 polymorphism was associated with the efficacy of GCs (dominant model: crude *OR*=0.514, 95% *CI*=0.321-0.824, *P*=0.006; adjusted *OR*=0.513, 95% *CI*=0.317-0.831, *P*=0.007). After BH correction, there was no association between rs12426382 polymorphism and efficacy of GCs (P_{BH}=0.084). In haplotype analysis, the haplotype CCCGAACATCCC (*OR*=2.273, 95% *CI*=1.248-4.139, *P*=0.006) and CTGGGACGTTC (*OR*=0.436, 95% *CI*=0.208-0.916, *P*=0.025) showed significant associations with the efficacy of GCs. After corrected by BH method, CCCGAACATCCC was still associated with the efficacy of GCs (P_{BH}=0.048). The rs3794241, rs1165681, rs2722188, rs3794240 and rs10861147 polymorphisms were associated with the improvement of HRQoL among SLE patients ($P < 0.05$). But no association existed after the correction of BH method ($P > 0.05$). *Conclusions:* The results of this study demonstrated that HSP90B1 genetic polymorphisms might be associated with the efficacy of GCs, but not associated with the improvement of HRQoL in Anhui population with SLE.

Keywords: Systemic lupus erythematosus, HSP90B1, polymorphism, glucocorticoids, health-related quality of life

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder affecting organ systems and causing multiple clinical symptoms [1], and it diminishes the quality of patients' life. Even to this day, we have not yet grasped the full etiology of SLE, but its aetio-

logical agents are really multifactorial. Environmental as well as genetic factors are likely to contribute to the development of SLE [2]. China was reported with relatively higher prevalence rate as 97.5 to 100/100,000 when compared to other ethnicities, and SLE is going to bring heavier burden to China in the near future [3]. Earlier diagnostic approaches and more appropriate treatment strategies have dramatically improved the survival of SLE in last 50 years [4]. Unfortunately, the risk of death for SLE patients is still 2 times higher than that of general population [5]. Treatment of SLE is still a challenge because there are no interventions resulting in a cure. Glucocorticoids (GCs) are widely used in clinic therapy at present and exert their biological effects through glucocorticoid receptor (GR). GR is a member of the nuclear hormone receptor super family of ligand-activated transcription factors [6] and depends on the heat shock proteins 90 (HSP-90) molecular chaperone for in vivo function [7].

Heat shock proteins (HSPs), first discovered in 1962 by Ritossa, are a set of ubiquitous and highly conserved proteins, and they are a family of highly conserved proteins and grouped together according to sequence homology and molecular size. Under stress conditions, HSPs which act as chaperones and cytoprotective agents are induced [8]. Heat shock protein 90 kDa beta member 1 (HSP90B1) gene, a member of HSP90 family of stress proteins which is located on chromosome 12q23.3, encodes 94-kDa glucose-regulated protein 94 (GRP-94) which is also naned 96-kDa heat shock glycoprotein (gp96). It has been described that gp-96 was closely related to antitumor immunity and antitumor immunological characters. Recent studies have shown that gp96 might promote the chronic inflammation of rheumatoid arthritis (RA) and was identified as a potential new therapeutic target [9]. In the animal experiment, the SLE model mice resulted from chronic cell surface exposure of gp96; then the model mice were offered a chemical compound that binds and suppresses surface presentation of gp96, and the SLE-associated symptoms of these mice were alleviated. This model mice study suggested gp96 as a potential therapeutic target to treat autoimmune diseases like SLE [10].

SLE affects multiple organs and leads to poor health-related quality of life (HRQoL). HRQoL is a multi-dimensional construct that encompasses the physical and mental domains, and should be examined in addition to disease activity and accumulated damage in evaluating the prognosis of SLE. The 36-item Short Form health survey (SF-36) is a generic quality of life questionnaire that has been widely used in SLE.

In our previous study, HSP90AA1, one member of HSP90 family, gene polymorphisms influence response to GCs in SLE patients treatment [11] and our previous case-control study has showed that HSP90B1 gene polymorphisms (rs1165681) may be associated with the susceptibility of SLE in Anhui population [12]. Therefore, this study was performed to investigate the association of HSP90B1 genetic polymorphisms with response to GCs in patients with SLE. In addition, we examined whether HSP90B1 gene polymorphisms were associated with the improvement of HRQoL among patients with SLE.

Material and methods

Patients and treatment

This study was carried out with the permission of the ethical committee of Anhui Medical University. After detailed explanation of the study, each subject was required to sign on written informed consent. SLE patients were recruited from the First Affiliated Hospital and the Second Affiliated Hospital of Anhui Medical University, and they all met the revised criteria for the classification of SLE established by the American College of Rheumatology (ACE) in 1997 [13]. Two rheumatologists made diagnoses and the results were confirmed by third rheumatologist. In baseline, scores on the SLE disease activity index (SLEDAI) of these patients were ≥ 5, and no patients had taken GCs in the nearly three months. Potential SLE patients were excluded: patients with lupus crisis or requiring GCs plus therapy, and those who were pregnant or lactating, patients with contraindications to GCs or who were allergic to hydroxychloroquine. Besides, SLE patients suffering from other rheumatic disease or tumors meanwhile were excluded.

Table 1. Tag SNPs information and primer sequence used for genotyping

Polymorphisms	Location	Allele		Primer
rs3794241	Chr12: 104, 329, 433	C/T	rs3794241F	TTTCCTGTTTTTACTGCAGCAGATGT
			rs3794241R	GAGGGCACTGGGGCATAACTCT
rs1165681	Chr12: 104, 325, 111	C/T	rs1165681F	AAGGCCGAAGTTTTGGCTTGAT
			rs1165681R	CGGGCAAACTCTTCAACATCAC
rs17034931	Chr12: 104, 325, 459	C/G	rs17034931F	TGTTGAAGAGTTTGCCCGTGTT
			rs17034931R	TGCTCCACAGTGAGGACTTCAAAA
rs2722188	Chr12: 104, 325, 649	G/T	rs2722188F	TGTTGAAGAGTTTGCCCGTGTT
			rs2722188R	TGCTCCACAGTGAGGACTTCAAAA
rs10778306	Chr12: 104, 325, 725	A/G	rs10778306F	TGTTGAAGAGTTTGCCCGTGTT
			rs10778306R	TGCTCCACAGTGAGGACTTCAAAA
rs17034938	Chr12: 104, 329, 212	A/G	rs17034938F	GACAGGGCAGCTTTTTGCCTTT
			rs17034938R	GAACATCTGCTGCAGTAAAAACAGGA
rs3794240	Chr12: 104, 329, 541	A/C	rs3794240F	AGTTATGCCCCAGTGCCCTCTC
			rs3794240R	TTGGGAATGGAGCTTCCAACAA
rs17034943	Chr12: 104, 329, 950	A/G	rs17034943F	ACGGCCTCAGGTTCCATCTCTA
			rs17034943R	ACCACACTTGGCTGGGACACAT
rs10861147	Chr12: 104, 330, 515	C/T	rs10861147F	AAAATTTCTAATGGGTGCCAGCTGTA
			rs10861147R	GCCCCTGGTCTCAGAGCACAT
rs12426382	Chr12: 104, 333, 828	C/T	rs12426382F	TTGGTTTCCAGAACACACCATTTTT
			rs12426382R	TTTCATGTTTTACGGGTTTTGTGGT
rs1165687	Chr12: 104, 334, 193	A/C	rs1165687F	TGTGAGATCCTATGCCTGGGAATAAT
			rs1165687R	TGAAGGCAGAACCAACAGTGTTTTA
rs1177457	Chr12: 104, 336, 127	C/T	rs1177457F	GCCACCTTTTTATCAAGCCTTTCATT
			rs1177457R	GGTGAAGCACTCCAATTCATTCAGA

The SLE patients took oral GCs and the starting dose of GCs was determined by the rheumatologists according to the degree of disease activity, in general, patients with total scores on the SLEDAI less than 10 at the start of the study received GCs (prednisone) therapy 10 mg/day-0.5 mg/kg/day and those with total scores on the SLEDAI more than 10 received GCs (prednisone) therapy 0.5-1.0 mg/kg/day. SLE patients also received oral hydroxychloroquine therapy (200 mg-400 mg). During the treatment, the dosage adjustments of drugs were determined by the rheumatologists after the consultation. The treatment effects of enrolled patients were estimated by SLEDAI at baseline and 4, 8, 12 weeks.

Efficacy of GCs assessment

According to response to GCs measured by SLEDAI scores, these participants were classified into two groups. The classification criteria for the sensitive group was that the total SLEDAI score was ≤ 4 at 12 weeks or the reduced score compared with baseline was ≥ 5. And the classification criteria for the insensitive group was that the total SLEDAI score was > 4 at 12 weeks and the reduced score compared with baseline was < 5. In the course of treatment, subjects, who received other immunosuppressants because of lack of efficacy, were also considered as GCs-insensitive patients.

Tag SNP selection and genotyping

Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood by using Blood Genome DNA Extraction Kit (QIAGEN, Germany) according to manufacturer's instructions. DNA samples were stored at -80°C until they were used. Genotype determination was performed by using Multiplex SNaPshot technology, an ABI fluorescence-based assay allelic discrimination method (Applied Biosystems, Foster City, CA).

The method was used to selected HSP90B1 SNPs which was performed in previous study [12]. HapMap database for CHB (Chinese Han

Table 2. Demographic characteristics of patients between sensitive group and insensitive group

Characteristics	Sensitive Group (n=160)	Insensitive Group (n=131)	*P*-value
Age (years)	34.75±11.97	35.68±11.45	0.500
Body Mass Index (kg/m^2)	20.83±3.27	21.07±2.79	0.508
SLEDAI scores	11.65±2.31	11.02±2.79	0.038
Dose of GCs (mg/d)	44.53±15.98	39.96±17.66	0.021
Gender			0.950
Male	15 (9.38)	12 (9.16)	
Female	145 (90.62)	119 (90.84)	
Marital status			0.841
Married	123 (76.88)	102 (77.86)	
Unmarried	37 (23.12)	29 (22.14)	
Smoking			0.350
No	150 (93.75)	126 (96.18)	
Yes	10 (6.25)	5 (3.82)	
Drinking			0.930
No	141 (88.12)	115 (87.79)	
Yes	19 (11.88)	16 (12.21)	

in Beijing) sample (release No. 24/phaseII Nov08, on NCBI B36 assembly) was applied to retrieve single nucleotide polymorphisms (SNPs) in HSP90B1 gene, and 38 SNPs were retrieved. Tag SNPs were selected by using Haploview software (4.0 version) according to linkage Disequilibrium (LD) graph. The criteria for selecting tag SNPs were $r^2 > 0.8$ and minor allele frequency (MAF) > 0.01. Finally, we selected 12 tag SNPs: rs3794241, rs1165681, rs17034931, rs2722188, rs10778306, rs17034938, rs3794240, rs17034943, rs10861147, rs12426382, rs1165687 and rs1177457 (**Table 1**).

Health-related quality of life assessment

We used SF-36 questionnaire to assess SLE patients' HRQoL in the following eight scales: physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE), and mental health (MH). The eight scales were calculated into two summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS) [14]. These patients' HRQoL were assessed at baseline and 12 weeks respectively and the scores of the total, PF, RP, BP, GH, VT, SF, RE, MH, PCS and MCS were counted in the two periods. The improvement score was equal to 12 weeks score subtracts baseline score.

Statistical analysis

Mean and standard deviation (SD) were used to describe normally distributed continuous variables; median (M) and interquartile range (P_{25}-P_{75}) were used to describe non-normally distributed continuous variables; categorical variables were presented as number and percentage. *t*-test was used to evaluate normally distributed data for quantitative comparisons; non-parametric statistics were used if the data followed skewed distribution; Chi-squared test was used on categorical data. The association of the efficacy of GCs with HSP90B1 gene polymorphisms was examined by using univariate and multivariate regression analysis (Y: Sensitive=0, Insensitive=1). Multivariate logistic regression models were adjusted for potential confounding factors, including age, sex, body mass index (BMI), smoking status, alcohol consumption, baseline SLEDAI scores and dose of GCs. Odds ratios (*OR*s) and 95% confidence intervals (95% *CI*s) were calculated according to Woolf's method. The quality of the genotype data was assessed by Hardy-Weinberg equilibrium test. The haplotype analysis was performed by online software SHEsis (http://analysis.bio-x.cn), and haplotype frequencies < 0.03 were not listed in result. Benjamini & Hochberg (BH) method was used for multiple testing correction based on false discovery rate (FDR) by R-3.1.2 software. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, IL). All *P* values less then 0.05 were considered to be statistically significant.

Results

Demographic and clinical characteristics, treatment response, genotype frequencies

A total of 305 patients participated in the follow-up visits, but 14 (4.59%) patients were excluded from the study because of loss to follow-up. Thus, 291 (95.41%) patients were included in the final data analyses. Of these patients, 160 (54.98%) were considered as GCs-sensitive group, and 131 (45.02%) were considered GCs-insensitive. In insensitive group, 23 patients received other immunosup-

Table 3. Genotype frequencies of polymorphisms in HSP90B1 gene between sensitive group and insensitive group and results of HWE

Polymorphisms (Minor Allele)	Sensitive Group (n=160)			Insensitive Group (n=131)			*P*-value for HWE
	Wild type	Heterozygous	Homozygous mutants	Wild type	Heterozygous	Homozygous mutants	
rs3794241 (T)	101 (63.13)	53 (33.12)	6 (3.75)	80 (61.07)	42 (32.06)	9 (6.87)	0.584
rs1165681 (T)	45 (28.12)	82 (51.25)	33 (20.63)	49 (37.41)	57 (43.51)	25 (19.08)	0.611
rs17034931 (C)	101 (63.13)	53 (33.12)	6 (3.75)	85 (64.89)	36 (27.48)	10 (7.63)	0.223
rs2722188 (T)	109 (68.13)	49 (30.62)	2 (1.25)	92 (70.23)	37 (28.24)	2 (1.53)	0.12
rs10778306 (G)	73 (45.62)	76 (47.50)	11 (6.88)	76 (58.02)	45 (34.35)	10 (7.63)	0.596
rs17034938 (G)	129 (80.63)	29 (18.12)	2 (1.25)	105 (80.15)	24 (18.32)	2 (1.53)	0.616
rs3794240 (A)	75 (46.88)	80 (50.00)	5 (3.12)	71 (54.20)	49 (37.40)	11 (8.40)	0.066
rs17034943 (G)	45 (28.12)	84 (52.50)	31 (19.38)	49 (37.40)	62 (47.33)	20 (15.27)	0.659
rs10861147 (C)	111 (69.38)	47 (29.37)	2 (1.25)	91 (64.47)	37 (28.24)	3 (2.29)	0.262
rs12426382 (T)	74 (46.25)	75 (46.88)	11 (6.87)	82 (62.60)	43 (32.82)	6 (4.58)	0.749
rs1165687 (A)	159 (99.38)	1 (0.62)	0 (0)	130 (99.24)	1 (0.76)	0 (0)	0.953
rs1177457 (T)	35 (21.88)	96 (60.00)	29 (18.12)	36 (27.48)	62 (47.33)	33 (25.19)	0.138

pressive agents due to lack of efficacy. The demographic characteristics of these patients in two group were no statistical differences (**Table 2**). There was no significant difference in age, body mass index (BMI), gender, marital status, tobacco and alcohol consumption *(P* > 0.05) except baseline SLEDAI scores and dose of GCs (*P* < 0.05) between sensitive group and insensitive group. Other clinic characteristics including photosensitivity, malar rash, discoid rash, oral ulcers, serositis, renal disorder, arthritis hair loss and hematologic disorder were presented , and there were no statistical differences between two groups (*P* > 0.05) (Table S1). The genotype frequencies of 12 SNPs were evaluated and reported and all of SNPs were in Hardy-Weinberg equilibrium (*P* > 0.05) and were included in follow analysis (**Table 3**).

Association between efficacy of GCs and HSP90B1 genetic polymorphisms

Univariable and multivariable logistic regression analyses were used to discriminate the impact of SNPs of HSP90B1 gene on the response of SLE patients to GCs treatment (GCs-sensitive=0, GCs-insensitive=1). Results showed that the rs12426382 polymorphism was associated with the efficacy of GCs (dominant model: crude *OR*=0.514, 95% *CI*=0.321-0.824, *P*=0.006; adjusted *OR*=0.513, 95% *CI*=0.317-0.831, *P*=0.007). A marginal association was found between the rs10778306 polymorphism and the efficacy of GCs (dominant model: crude *OR*=0.607, 95% *CI*=0.381-0.968, *P*=0.036; adjusted *OR*=0.640, 95% *CI*=0.398-1.031, *P*=0.067). Corrected by BH method, the results showed that no SNPs were associated with the efficacy of GCs (**Table 4**).

Haplotype analysis for SNPs of HSP90B1 gene

To estimate the relationship of HSP90B1 haplotypes and GCs efficacy, haplotype analysis was performed. Haplotype frequencies < 0.03 were ignored in the analysis. We observed eight haplotypes combinations, and found significant associations in the distribution of the haplotype frequencies between insensitive group and sensitive group (*P* < 0.05). The haplotype CCCGAACATCCC was associated with worse GCs efficacy (*OR*=2.273, 95% *CI*=1.248-4.139, *P*=0.006) and the haplotype CTGGGACGTTCC was associated with better GCs efficacy (*OR*=0.436, 95% *CI*=0.208-0.916, *P*=0.025). After BH correction, the haplotype CCCGAACATCCC was still associated with GCs efficacy (P_{BH}=0.048) (**Table 5**).

HSP90B1 gene polymorphisms and improvement in HRQoL

We found that rs3794241, rs1165681, rs2722188, rs3794240 and rs10861147 polymorphisms were related to the improvement of HRQoL. There was association between rs3794241 polymorphism and improvement in role-emotional (RE) and Mental Component Summary (MCS). Patients with heterozygous or homozygous mutant genotypes had better im-

Table 4. Association of glucocorticoids efficacy and polymorphisms of HSP90B1 gene

SNPs	Dominant Model					Recessive Model				
	Crude *OR (95% CI)*	Crude *P*-value	Adjusted *OR (95% CI)*	Adjusted *P*-value	P_{BH}	Crude *OR (95% CI)*	Crude *P*-value	Adjusted *OR (95% CI)*	Adjusted *P*-value	P_{BH}
rs3794241	1.091 (0.678-1.757)	0.719	1.089 (0.664-1.785)	0.735	0.922	1.893 (0.656-5.464)	0.238	1.888 (0.641-5.557)	0.249	0.685
rs1165681	0.655 (0.400-1.073)	0.093	0.872 (0.531-1.432)	0.142	0.389	0.908 (0.508-1.622)	0.744	0.927 (0.509-1.689)	0.804	0.966
rs17034931	0.927 (0.572-1.500)	0.756	0.854 (0.518-1.406)	0.587	0.922	2.121 (0.750-6.000)	0.156	1.944 (0.661-5.712)	0.227	0.685
rs2722188	0.906 (0.549-1.495)	0.700	0.910 (0.543-1.523)	0.719	0.922	1.226 (0.170-8.827)	0.839	1.400 (0.179-10.935)	0.748	0.966
rs10778306	0.607 (0.381-0.968)	0.036	0.640 (0.398-1.031)	0.067	0.380	1.120 (0.460-2.725)	0.803	1.065 (0.426-2.660)	0.893	0.966
rs17034938	1.030 (0.576-1.843)	0.920	1.105 (0.606-2.015)	0.744	0.922	1.226 (0.170-8.827)	0.839	1.044 (0.142-7.655)	0.966	0.966
rs3794240	0.746 (0.469-1.185)	0.214	0.712 (0.442-1.146)	0.162	0.389	1.226 (0.170-8.827)	0.059	2.700 (0.890-8.198)	0.079	0.605
rs17034943	0.655 (0.400-1.073)	0.093	0.647 (0.387-1.079)	0.095	0.380	0.750 (0.405-1.389)	0.360	0.783 (0.416-1.474)	0.449	0.706
rs10861147	0.996 (0.603-1.644)	0.987	1.026 (0.612-1.719)	0.922	0.933	1.851 (0.305-11.248)	0.504	2.201 (0.337-14.399)	0.410	0.706
rs12426382	0.514 (0.321-0.824)	0.006	0.513 (0.317-0.831)	0.007	0.084	0.650 (0.234-1.808)	0.409	0.601 (0.211-1.712)	0.340	0.706
rs1165687	1.225 (0.076-19.770)	0.886	1.177 (0.070-19.834)	0.910	0.922	-	-	-	-	
rs1177457	0.739 (0.432-1.263)	0.269	0.736 (0.424-1.278)	0.276	0.552	1.521 (0.866-2.672)	0.145	1.608 (0.898-2.879)	0.110	0.605

Table 5. Haplotype analysis for SNPs of HSP90B1 gene and glucocorticoids efficacy

Haplotypes	Frequency of Insensitive Group	Frequency of Sensitive Group	X^2-value	Pearson's *P*-value	P_{BH}	*OR (95% CI)*
CCCGAAAATCCC	16.31 (0.062)	24.73 (0.077)	0.112	0.738	0.738	0.894 (0.464-1.724)
CCCGAACATCCC	30.34 (0.116)	20.18 (0.063)	7.491	0.006	0.048	2.273 (1.248-4.139)
CCGGAACATCCT	50.09 (0.191)	64.39 (0.201)	0.155	0.694	0.738	1.091 (0.708-1.680)
CTGGGAAGTTCC	22.07 (0.084)	19.10 (0.060)	2.430	0.119	0.317	1.664 (0.873-3.171)
CTGGGACGTTCC	10.12 (0.039)	29.63 (0.093)	5.032	0.025	0.100	0.436 (0.208-0.916)
CTGGGGCATCCC	11.71 (0.045)	11.67 (0.036)	0.631	0.427	0.584	1.401 (0.608-3.226)
CTGTAACGCCCT	21.50 (0.082)	35.84 (0.112)	0.600	0.438	0.584	0.798 (0.450-1.414)
TCGGAACATCCT	16.14 (0.062)	16.05 (0.050)	0.898	0.343	0.584	1.414 (0.689-2.902)

provement in RE and MCS compared with wild genotype (RE, 0 (0-0) vs 0 (0-33.33), *P*=0.029; MCS, 2.13 (-1.63-8.75) vs 4.75 (-0.50-16.21), *P*=0.041). The rs1165681 polymorphism was associated with improvement in bodily pain (BP) and social function (SF). Patients with wild or heterozygous mutants genotype had better improvement in BP and SF compared with homozygous mutant genotype (BP, 12.00 (0-26.00) vs 0 (0-22.00), *P*=0.035; SF, 0 (0-12.50) vs 0 (0-12.50), *P*=0.018). We also found that rs2722188 polymorphism had a significant association with improvement in total score of SF-36, bodily pain (BP), Physical Component Summary (PCS). Patients with homozygous mutants genotype had worse improvement in total score, BP, PCS compared with wild or heterozygous mutants genotypes (total score, -1.41 (-10.13-0.63) vs 6.06 (0.13-14.50), *P*=0.029; BP, -3.00 (-16.00-0) vs 11.00 (0-26.00), *P*=0.027; PCS, -0.75 (-9.50-0.50) vs 8.75 (1.25-19.25), *P*=0.025). The improvement of total score, vitality (VT) and Mental Component Summary (MCS) had a relationship with rs3794240 polymorphism. Patients with heterozygous or homozygous mutant genotypes had better improvement in total score and MCS compared with wild genotype (total score, 7.94 (1.75-17.13) vs 4.16 (-1.13-10.56), *P*=0.027; MCS, 3.50 (-0.50-11.21) vs 1.69 (-2.25-9.58), *P*=0.042). But patients with wild or heterozygous mutants genotype had better improvement in VT compared with homozygous mutant genotype (0 (-5.00-10.00) vs 0 (-5.00-0), *P*=0.047). The rs10861147 polymorphism was found to be associated with the improvement in bodily pain (BP) and Physical Component Summary (PCS). Patients with wild or heterozygous mutants genotypes had better improvement in BP and PCS compared with homozygous mutant genotype (BP, 11.00 (0-26.00) vs 0 (-6.00-0), *P*=0.020; PCS, 8.50 (1.25-19.25) vs -0.25 (-1.25-1.25), *P*=0.048). However, after corrected by BH method, we found no SNPs were associated with the improvement of HRQoL (*P* > 0.05) (**Table 6**).

Discussion

Although GCs are widely used drugs during SLE treatment, there are many patients less responsive to the therapy [15]. While the reason for this common phenomenon is still not understood, it is becoming clear that genetic variations could underlie the difference in responsiveness to GCs in SLE patients. In our previous study, the associations of gene polymorphisms within HSP90AA1 gene with the efficacy of GCs in Chinese population with SLE have been reported [11]. HSP90B1 is located on chromosome 12q23.3 and genome-wide association study (GWAS) have identified susceptibility loci (12q23-24) for SLE in Chinese Han population [16] and our study has found that rs1165681 within HSP90B1 gene was associated with SLE [12]. Therefore, this study was further performed to identify the association of the efficacy of GCs with HSP90B1. Results showed that HSP90B1 gene (rs12426382) had marginal association with the response of GCs, and haplotype analysis indicated that the haplotypes CCCGAACATCCC was associated with the efficacy of GCs.

GCs exert their biological effects through GR and the glucocorticoid-GR complex is translocated to the nucleus; then the complex triggers transactivation as well as trans-repression of glucocorticoid-responsive genes finally resulting in the induction of programmed cell death [6]. GR has three domain structures: an amino-

Table 6. Comparison of improvement in health-related quality of life patients between genotypes

SNP	Dominant model				Recessive model			
	Wild	Heterozygous/ homozygous mutant	*P*-value	P_{BH}	Wild/ heterozygous	Homozygous mutants	*P*-value	P_{BH}
rs3794241	181 (62.20)	110 (37.80)			276 (94.85)	15 (5.15)		
Total score	5.00 (-0.94-11.29)	7.97 (0.81-17.94)	0.075	0.275	5.69 (0.06-13.61)	13.81 (1.88-24.50)	0.232	0.843
Physical function	5.00 (0-25.00)	10.00 (0-25.00)	0.426	0.484	7.50 (0-25.00)	10.00 (0-20.00)	0.604	0.845
Role-physical	0 (0-0)	0 (0-50.00)	0.133	0.366	0 (0-0)	0 (0-100.00)	0.052	0.572
Bodily pain	11.00 (0-26.00)	10.00 (0-23.00)	0.440	0.484	10.00 (0-26.00)	10.00 (0-29.00)	0.890	0.890
General health	0 (0-5.00)	5.00 (0-10.00)	0.209	0.396	5.00 (0-5.00)	5.00 (-10.00-20.00)	0.691	0.845
Vitality	0 (-5.00-10.00)	0 (0-10.00)	0.359	0.484	0 (-5.00-10.00)	0 (-10.00-15.00)	0.674	0.845
Social function	0 (0-12.50)	0 (0-12.50)	0.440	0.484	0 (0-12.50)	0 (-12.50-12.50)	0.401	0.843
Role-emotional	0 (0-0.00)	0 (0-33.33)	0.029	0.226	0 (0-0)	0 (0-100.00)	0.396	0.843
Mental health	0 (-4.00-4.00)	0 (-4.00-4.00)	0.883	0.883	0 (-4.00-4.00)	-4.00 (-8.00-4.00)	0.460	0.843
Physical componen summary	6.75 (0.50-16.25)	11.88 (0.25-19.75)	0.216	0.396	7.75 (0.38-17.75)	18.00 (3.75-35.75)	0.143	0.787
Mental component summary	2.13 (-1.63-8.75)	4.75 (-0.50-16.20)	0.041	0.226	2.79 (-1.06-10.67)	2.13 (-4.13-24.00)	0.786	0.865
rs1165681	94 (32.30)	197 (67.70)			233 (80.07)	58 (19.93)		
Total score	6.13 (0.81-14.50)	5.63 (-1.88-14.13)	0.710	0.979	5.79 (0-14.19)	6.53 (0.75-17.13)	0.762	0.946
Physical function	10.00 (0-25.00)	5.00 (0-25.00)	0.239	0.979	5.00 (0-25.00)	10.00 (0-25.00)	0.947	0.947
Role-physical	0 (0-25.00)	0 (0-0)	0.495	0.979	0 (0-25.00)	0 (0-0)	0.897	0.947
Bodily pain	10.00 (0-26.00)	11.00 (0-23.00)	0.979	0.979	12.00 (0-26.00)	0 (0-22.00)	0.035	0.193
General health	0 (0-5.00)	5.00 (0-10.00)	0.397	0.979	5.00 (0-5.00)	2.50 (-5.00-10.00)	0.683	0.946
Vitality	0 (-5.00-10.00)	0 (0-10.00)	0.764	0.979	0 (-5.00-10.00)	5.00 (0.00-10.00)	0.091	0.334
Social function	6.25 (0-12.50)	0 (0-12.50)	0.055	0.605	0 (0-12.50)	0 (0-12.50)	0.018	0.193
Role-emotional	0 (0-33.33)	0 (0-0)	0.930	0.979	0 (0-0)	0 (0-33.33)	0.230	0.618
Mental health	0 (-4.00-4.00)	0 (-4.00-4.00)	0.938	0.979	0 (-4.00-4.00)	0 (-4.00-4.00)	0.774	0.946
Physical component summary	8.38 (1.25-19.50)	7.75 (0.25-18.75)	0.721	0.979	8.00 (0.50-19.50)	7.63 (1.25-17.00)	0.592	0.946
Mental component summary	3.50 (-1.00-10.87)	2.13 (-1.25-10.88)	0.572	0.979	2.25 (-1.25-10.58)	4.98 (-1.00-13.75)	0.281	0.618
rs2722188	201 (69.07)	90 (30.93)			287 (98.63)	4 (1.37)		
Total score	6.06 (0.75-14.66)	5.56 (-1.13-11.06)	0.226	0.413	6.06 (0.13-14.50)	-1.41 (-10.13-0.63)	0.029	0.106
Physical function	10 (0-25)	5.00 (0-25.00)	0.335	0.461	10.00 (0-25.00)	0 (-15.00-5.00)	0.099	0.143
Role-physical	0 (0-25.00)	0 (0-0)	0.079	0.300	0 (0-25.00)	0 (0-0)	0.461	0.521
Bodily pain	11.00 (0-26.00)	10.00 (0-23.00)	0.414	1.000	11.00 (0-26.00)	-3.00 (-16.00-0)	0.027	0.106
General health	5.00 (0-10.00)	0 (-5.00-5.00)	0.191	0.413	5.00 (0-10.00)	-5.00 (10.00-0)	0.104	0.143
Vitality	0 (-5.00-10.00)	5.00 (0-10.00)	0.075	0.300	0 (-5.00-10.00)	-5.00 (-17.50-0)	0.057	0.136
Social function	0 (0-12.50)	0 (0-12.50)	0.263	0.413	0 (0-12.50)	-6.25 (-12.50-0)	0.074	0.136
Role-emotional	0 (0-33.33)	0 (0-0)	0.109	0.300	0 (0-0)	0 (0-0)	0.474	0.521
Mental health	0 (-4.00-4.00)	0 (-4.00-8.00)	0.776	0.854	0 (-4.00-4.00)	0 (-18.00-8.00)	0.724	0.724
Physical component summary	8.00 (1.25-19.50)	7.88 (-0.25-14.00)	0.104	0.300	8.75 (1.25-19.25)	-0.75 (-9.50-0.50)	0.025	0.106
Mental component summary	2.88 (-1.25-10.88)	2.31 (-1.00-10.25)	0.667	0.815	2.88 (-1.13-10.88)	-2.81 (-10.75-0.75)	0.074	0.136
rs3794240	146 (50.17)	145 (49.83)			275 (94.50)	16 (5.50)		

Total score	4.16 (-1.13-10.56)	7.94 (1.75-17.13)	0.027	0.132	5.81 (0.13-14.19)	4.69 (0.63-14.58)	0.862	0.882
Physical function	5.00 (0-25.00)	10.00 (0-25.00)	0.271	0.336	10.00 (0-25.00)	5.00 (0-15.00)	0.523	0.882
Role-physical	0 (0-0)	0 (0-50.00)	0.058	0.132	0 (0-25.00)	0 (0-37.50)	0.354	0.882
Bodily pain	10.00 (0-23.00)	11.00 (0-26.00)	0.399	0.439	10.00 (0-26.00)	5.00 (0-18.50)	0.367	0.882
General health	0 (-5.00-5.00)	5.00 (0-10.00)	0.141	0.253	5.00 (0-10.00)	2.50 (0-7.50)	0.878	0.882
Vitality	0 (-5.00-10.00)	0 (0-10.00)	0.275	0.336	0 (-5.00-10.00)	0 (-5.00-0)	0.047	0.517
Social function	0 (0-12.50)	0 (0-12.50)	0.161	0.253	0 (0-12.50)	0 (0-12.50)	0.882	0.882
Role-emotional	0 (0-0)	0 (0-33.33)	0.059	0.132	0 (0-0)	0 (0-33.33)	0.149	0.820
Mental health	0 (-4.00-4.00)	0 (-4.00-4.00)	0.679	0.679	0 (-4.00-4.00)	0 (-4.00-4.00)	0.753	0.882
Physical component summary	6.25 (0-15.00)	10.25 (1.25-21.75)	0.06	0.132	8.25 (0-19.25)	6.00 (0.13-18.88)	0.873	0.882
Mental component summary	1.69 (-2.25-9.58)	3.50 (-0.50-11.21)	0.042	0.132	2.50 (-1.25-2.50)	3.98 (-.63-10.79)	0.566	0.882
rs10861147	202 (69.42)	89 (30.58)			286 (98.28)	5 (1.72)		
Total score	5.97 (0.75-14.50)	5.63 (-1.13-14.13)	0.287	0.526	5.97 (0.13-14.38)	0.38 (-3.19-0.88)	0.130	0.464
Physical function	5.00 (0-25.00)	10.00 (0-25.00)	0.886	0.886	10.00 (0-25.00)	0 (0-10.00)	0.238	0.464
Role-physical	0 (0-25.00)	0 (0-0)	0.150	0.526	0 (0-25.00)	0 (0-0)	0.409	0.464
Bodily pain	10.00 (0-26.00)	11.00 (0-26.00)	0.765	0.842	11.00 (0-26.00)	0 (-6.00-0)	0.02	0.22
General health	5.00 (0-10.00)	5.00 (-5.00-5.00)	0.528	0.645	5.00 (0-10.00)	-5.00 (-5.00-5.00)	0.351	0.464
Vitality	0 (-5.00-10.00)	5.00 (0-10.00)	0.259	0.526	0 (-5.00-10.00)	0 (-10.00-0)	0.360	0.464
Social function	0 (0-12.50)	0 (0-12.5)	0.058	0.526	0 (0-12.50)	0 (-12.50-0)	0.210	0.464
Role-emotional	0 (0-0)	0 (0-0)	0.199	0.526	0 (0-0)	0 (0-0)	0.422	0.464
Mental health	0 (-4.00-4.00)	0(-4.00-8.00)	0.497	0.645	0 (-4.00-4.00)	8.00 (-8.00-8.00)	0.658	0.658
Physical component summary	7.88 (1.25-19.25)	8.75 (-0.25-17.00)	0.273	0.526	8.50 (1.25-19.25)	-0.25 (-1.25-1.25)	0.048	0.264
Mental component summary	3.13 (-1.00-10.88)	2.00 (-2.50-10.25)	0.359	0.564	2.88 (-1.13-10.88)	-0.50 (-5.13-2.00)	0.313	0.464

terminal transactivating domain, a DNA-binding domain, and a carboxy-terminal ligand-binding domain which consists of specific steroid and HSP90 binding sites [17]. Thus it can be seen that GR may depend on HSP90 molecular chaperone for in vivo function. HSP90B1 gene, encoding gp96 (also named GRP-94), is one member of HSP90 family. In normal physiological conditions, Gp96 is mainly located in the lumen of endoplasmic reticulum (ER), and shares high homology at the amino acid level with human cytosolic HSP90 [18]. Gp96 also shares many biochemical features with other HSP90 proteins, in particular its domain structure and ATPase activity [19]. Therefore, it is possible that gp96 may bind with GR in HSP90 binding sites and assists GR in forming active structure and make GR fold correctly. In addition, gp96 is one of important molecular chaperone in ER. Cellular stress arises with misfolded proteins accumulating in ER when endogenous factors stimulate cell, this phenomenon is known as endoplasmic reticulum stress (ERS) [20]. ERS has close correlations with autoimmune diseases, including RA, myasthenia gravis (MG) and SLE. There was a study showing that the ER chaperone GRP78 was crucial for synoviocyte proliferation and angiogenesis, the pathological hallmark of RA [21]. Suzuki *et al.* [22] proved that autoimmunity to ER chaperone gp96 is associated with a subset of MG patients who have additional autoimmune diseases. Anti-GRP94 autoantibodies have been observed in SLE patients [23]. Gp96, as one of ERS proteins, is expressed in the ER as well as occasionally at the cell surface, which play pathophysiological roles in autoimmune and inflammatory diseases [24]. Furthermore, evidence had shown that extracellular gp96 could serve as an endogenous dendritic cells (DCs) activator on an organismal level and chronic activation of DCs by gp96 may cause breakdown of peripheral tolerance, resulting in lupus-like autoimmune diseases [25]. Extracellular gp96 acts as a ligand of TLR2 and TLR4 and binds with them in recombinant N-terminal domain, resulting in activating the TLR signaling pathway secreting proinflammatory cytokine (IL-6 and TNF-α) [9]; Gp96 directly binds to CD91 and this complex gives rise to phosphorylating CD91 and activating NF-κB which modulate many molecules involving in immune response and inflammatory response [26]. Besides, animal experiment confirmed that surface translocation of gp96 can be chemically controlled and gp96 as a potential therapeutic target to treat autoimmune disease like SLE [10]. Gp96 maintains the stability of the environment inside the cell by ERS and activates the immune response through activating DCs. Therefore, gp96 may play an important role in SLE treatment. Based on the above evidence, it is possible that HSP90B1 genetic polymorphisms are associated with the the efficacy of GCs.

SLE, which is a complex disease, damages almost all systems and organs. The HRQoL of these patients may be affected by SLE seriously. Thumboo *et al.* [27] described that HRQoL in SLE patients was reduced when compared with the general population, and Furukawa *et al.* [28] also demonstrated that HRQoL was reduced in Japanese female patients with SLE. Previous study indicated that there was an association of GR gene genetic polymorphisms with improvement of HRQoL in Chinese SLE patients treated with GCs [29]. We found that HSP90B1 gene genetic polymorphisms were related to efficacy of GCs, then, we made further studies to explore whether association exists between genetic polymorphisms within HSP90B1 gene and improvement of HRQoL in Chinese SLE patients. Even thought there were similar studies finging that HRQoL is associated with the IL28B polymorphism in chronic hepatitis C (CHC) treated with pegylated interferon and ribavirin (RBV) [30] and the beta-2 adrenergic receptor (ADRB2) gene polymorphism is associated with the HRQoL of functional GI (FGID) [31], our results presented that there was no association between HSP90B1 gene and HRQoL. It's possible that the reduction of HRQoL measured by the SF-36 was associated with the disease damage but not with SLEDAI [32].

There are several limitations existing in our study. Firstly, lacking independent replication in different regions of China made it difficult to validate our results. We recruited SLE patients just from the First Affiliated Hospital and the Second Affiliated Hospital of Anhui Medical University in Anhui province of China. Subjects are limited and the geographic scope of extrapolation is restricted. Secondly, 14 patients were excluded from this study because of loss-to-follow-up. This may have little impact on our results. Thirdly, SLE patients participating in

the current study also took hydroxychloroquine. Hydroxychloroquine has slow onset of action (3-6 months), however, follow-up of the current study is 12 weeks and this leads to ineffective treatment on our participants.

Findings in this study suggest a minor relationship between HSP90B1 genetic polymorphisms and the efficacy of GCs, however, the association of HSP90B1 polymorphisms with improvement of HRQoL in Anhui SLE patients did not exist. Therefore, it's necessary to make further large-scale studies to confirm our results and explore the function sites within the HSP90B1 gene in SLE.

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Disclosure of conflict of interest

None.

Abbreviations

GCs, Glucocorticoids; ACE, American College of Rheumatology; BH, Benjamini & Hochberg; BMI, BodyMass Index; BP, Bodily Pain; CI, Confidence Interval; DNA, Deoxyribonucleic Acid; ER, Endoplasmic Reticulum; ERS, Endoplasmic Reticulum Stress; FDR, False Discovery Rate; GH, General Health; gp96, 96-kDa Heat Shock Glycoprotein; GR, Glucocorticoid Receptor; GRP-94, 94-kDa Glucose-regulated Protein 94; HRQoL, Health-related Quality of Life; HSP90, Heat Shock Proteins 90; HSP90B1, Heat Shock Protein 90 kDa Beta Member 1; HSPs, Heat Shock Proteins; LD, Linkage Disequilibrium; M, Median; MAF, Minor Allele Frequency; MCS, Mental Component Summary; MG, Myasthenia Gravis; MH, Mental Health; OR, OddsRatio; PCS, Physical Component Summary; PF, Physical Function; RA, Rheumatoid Arthritis; RE, Role-Emotional; RP, Role-Physical; SD, Standard Deviation; SF, Social Function; SF-36, 36-item Short Form Health Survey; SLE, Systemic Lupus Erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SNP, Single Nucleotide Polymorphism; VT, Vitality.

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Table S1. Clinical characteristics of patients between the sensitive group and insensitive group

Variables	Sensitive Group (n=160)	Insensitive Group (n=131)	*P*-value
Photosensitivity			0.707
No	93 (58.13)	79 (60.31)	
Yes	67 (41.87)	52 (39.69)	
Malar rash			0.260
No	64 (40.00)	61 (46.56)	
Yes	96 (60.00)	70 (53.44)	
Discoid rash			0.197
No	122 (76.25)	108 (82.44)	
Yes	38 (23.75)	23 (17.56)	
Oral ulcers			0.161
No	117 (73.12)	105 (80.15)	
Yes	43 (26.88)	26 (19.85)	
Serositis			0.521
No	142 (88.75)	113 (86.26)	
Yes	18 (11.25)	18 (13.74)	
Renal disorder			0.222
No	127 (79.37)	96 (73.28)	
Yes	33 (20.63)	35 (26.72)	
Arthritis			0.070
No	94 (58.75)	63 (48.09)	
Yes	66 (41.25)	68 (51.91)	
Hair loss			0.670
No	95 (59.38)	81 (61.83)	
Yes	65 (40.62)	50 (38.17)	
Hematologic disorder			0.545
No	64 (40.00)	57 (43.51)	
Yes	96 (60.00)	74 (56.49)	