Association of BCL2 polymorphisms and the IL19 single nucleotide polymorphism rs2243188 with systemic lupus erythematosus

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Abstract

Objective: Abnormal B cell lymphoma-2 (Bcl-2) and interleukin-19 (IL-19) expression is closely related to systemic lupus erythematosus (SLE) pathogenesis. We aimed to determine whether BCL2 polymorphisms and a single nucleotide polymorphism (SNP) of IL19 are significantly associated with SLE susceptibility and if this is affected by synergism between IL19 and BCL2 genotypes.

Methods: This observational cohort study randomly enrolled 150 patients with SLE and 150 healthy controls. Major BCL2 and IL19 allele and genotype distributions were examined in the two groups. The IL19 SNP rs2243188 was determined using the TaqMan-MGB probe method. The synergistic effect between BCL2 and IL19 and clinical symptoms of SLE was also analyzed.

Results: The distribution of major BCL2 genotypes and common BCL2 alleles, especially for genotypes 191, 193, and 197, differed significantly between patients and controls. A significant difference in the dominant genetic model was also observed between groups, but not in the recessive model. The risk of disease in individuals who carried both 195-bp BCL2 and 138-bp IL19 susceptibility alleles was higher than in those carrying either allele alone.

Conclusions: This preliminary study suggested that BCL2 polymorphisms and the IL19 SNP rs2243188 are closely related to the pathogenesis of SLE.

Keywords

B cell l-2, interleukin-19, single nucleotide polymorphism, systemic lupus erythematosus, synergism, genotype

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Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune connective tissue disease with multiple organ involvement. It is a heterogeneous disease with a highly variable etiology, involving genetic, epigenetic, and environmental factors. Factors such as sex, hormone levels, and dysfunctional apoptosis have been reported to play major roles in the pathogenesis of SLE. Moreover, abnormal expression levels of B cell lymphoma-2 (Bcl-2) and interleukin-19 (IL-19) were closely related to disease pathogenesis in Chinese patients.

The Bcl-2 family comprises a variety of repressor and activator proteins that regulate apoptosis, and interactions between pro- and anti-apoptotic members determine cell survival. The overexpression of Bcl-2 in transgenic mice was found to protect B cells against apoptosis, improve cell survival, and promote the development of a lupus-like autoimmune syndrome involving nephritis and autoantibody production including anti-dsDNA and anti-Sm antibodies.

IL-19 is a newly discovered pro-inflammatory cytokine and a member of the IL-10 cytokine family. The single nucleotide polymorphism rs2243188 in the 3' untranslated region of IL19 contains regulatory elements necessary for the normal expression of many genes. Furthermore, several studies have confirmed that IL19 rs2243188 is associated with genetic susceptibility to autoimmune diseases such as rheumatoid arthritis, vitiligo, psoriasis, ulcerative colitis, and lupus nephritis (LN). However, whether synergism between IL19 and BCL2 is associated with genetic susceptibility to SLE in the Chinese Han population has not been investigated.

In this study, correlations between BCL2 polymorphisms and the IL19 SNP rs2243188 with susceptibility to SLE were examined in patients with SLE and healthy controls.

Materials and methods

Subjects

Patients with SLE who were admitted to the Rheumatology Department of The Second Affiliated Hospital (SAH) of Zhejiang Chinese Medical University between July 2016 and July 2018 were eligible for enrollment. A total of 150 patients were randomly selected for inclusion in the study. A total of 150 healthy subjects were selected from the physical examination center of the hospital to comprise the control group. This control group was age- and sex-matched to patients with SLE. The study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of The SAH of Zhejiang Chinese Medical University in 2015 (approval number: 2015zjicm-016). Written informed consent was obtained from each patient.

Patients were included if they were: 1) aged over 18; and 2) met the revised SLE classification criteria of the American College of Rheumatology (1997). Controls were included if they: 1) did not meet any of the criteria for SLE; 2) had no history or direct family history of immune disease; 3) had no major illness or family history of illness; and 4) had no long-term use of glucocorticoids or immunosuppressive drugs. Patients were excluded if they had: 1) other serious systemic diseases; or 2) mental illness or other cognitive dysfunction rendering them unable to cooperate.

Patients were recruited through multiple advertising strategies, including posters at The SAH of Zhejiang Chinese Medical University and advertisements on official online medical media channels such as websites, Micro Blog, and WeChat sites of the Rheumatology Department of The SAH of Zhejiang Chinese Medical University.
Demographic information and blood sampling

This was an observational cohort study. General demographic information (sex, age, time since SLE diagnosis, education level, occupation, height, and weight), information about previous interventions and treatments, and current SLE occurrence was obtained from the participants.

Five milliliters of peripheral blood was collected from all participants, placed in an anti-coagulation tube, and protected from light and heat during transport (temperature controlled between 1°C and 4°C) to prevent dissolution. Genomic DNA was extracted from all samples with the Flexigene DNA Kit (Qiagen, Valencia, CA, USA) and stored at −80°C.

Genotyping

For BCL2 microsatellite primer design and synthesis, the serial number was entered in the BCL2 database to find BCL2 ends and a microsatellite marker 570 bp upstream of the ATG codon. BCL2 microsatellite amplification primers were: positive strand, 5'-CTGGGCATGGTGTTGCTGTTC-3' and negative strand, 5'-CAGGTGGTGTGGTCACGCAGCA-3'. Primers were dissolved in deionized water at 10 pmol/μL and stored in the dark at −20°C.

PCR reactions contained 0.2 μL of dNTPs, 0.2 μL of BCL2 positive strand primer, 0.2 μL of negative strand primer, 0.05 μL of Tsp DNA polymerase, 2.5 μL of DNA template, and 2.02 μL of deionized water. Cycle settings were 95°C for 2 minutes, followed by 35 cycles of 94°C for 1 minute, 60°C for 30 s, and 72°C for 15 s, with a final extension at 72°C for 9 minutes. PCR products were stored at 5°C.

Genotyping of the IL19 SNP rs2243188 was performed with a TaqMan SNP Genotyping Assay Kit (Thermo Fisher Scientific; USA) using an ABI7300 real-time PCR system (Applied Biosystems). Amplification was performed in a 10-μL reaction volume comprising 5 μL TaqMan Genotyping master mix, 0.1 μL TaqMan Genotyping assay mix, 0.9 μL ultrapure water, and 4 μL genomic DNA; the IL19 primer sequences were: positive strand, 5'-CTGGGCATGGTGTTGCTGTTC-3' and negative strand, 5'-CAGGTGGTGTGGTCACGCAGCA-3'.

A 5.8% Long Ranger denaturing gel was used to assess the amplification products. Each product was added to deionized water at a ratio of 1:10, and 1.5 μL or 3.5 μL of loading buffer was added. After denaturation at 95°C for 3 minutes, the samples were placed on ice, and 4 μL of each of the 36 samples was assessed. Electrophoresis and detection were performed using an ABI3730XL sequencer (Applied Biosystems, Foster City, CA, USA) with the following parameters: GeneScan mode, current, 20 mA; voltage, 1500 V; and power, 30 W. The temperature was controlled at 40°C, and 1× Tris borate buffer was added to the upper and lower electrophoresis tanks.

Fluorescent signals on the probes were collected and converted into electrophoretic images by GeneScan 3.1 software (Applied Biosystems; Foster City, CA, USA).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). The frequency (%) of count data and the intergroup rate were compared using the chi-square test. Results were corrected for multiple testing using the Bonferroni correction. The synergistic effect between BCL2 and IL19 was determined by logistic regression analysis. Differences were considered statistically significant at P < 0.01.
Results
Fifteen SLE patients were male and 135 were female, and their mean age was 41.25 ± 2.55 years. Eighteen healthy controls were male and 132 were female, and their mean age was 41.55 ± 2.45 years. There was no significant difference in age or sex distribution between patients and controls. Subject demographic information is shown in Table 1. All subjects were unrelated members of the Chinese Han population. The main clinical manifestations of patients with SLE were immunological disorders (n = 112; 74.7%), hematological disorders (n = 102; 68%), arthritis (n = 97; 64.7%), and renal disorders (n = 75; 50%) (Table 1).

Distribution of BCL2 allele frequencies
After Bonferroni correction, a significant difference was observed in the distribution of BCL2 genotypes 191, 193, and 197 between patients and controls (0.01/8; P < 0.001) (Table 2). No significant difference was found for BCL2 genotypes 189, 195, 199, 201, and 203 (0.01/8).

After Bonferroni correction, distribution of the BCL2 195/191-bp allele differed significantly between patients and controls (0.01/7; P < 0.001) (Table 3). No significant difference in distribution was observed for the BCL2 195/193-bp, 195/195-bp, 195/197-bp, 195/199-bp, 195/201-bp, or 195/203-bp alleles.

Distribution of IL19 rs2243188
The rs2243188 CC genotype frequency was found to be significantly higher than that of CA and AA genotype frequencies in patients and controls (P < 0.01) (Table 4). In the genetic model analysis, a significant difference was observed in the dominant pattern of IL19 rs2243188 between patients and controls (P < 0.05). However, there was no difference in the recessive model between

| Parameter                        | Patients with SLE (n = 150) | Healthy controls (n = 150) |
|----------------------------------|-----------------------------|---------------------------|
| Demographic characteristics      |                             |                           |
| Age (years)                      | 41.25 ± 2.55                | 41.55 ± 2.45              |
| Female, n (%)                    | 135 (90.00)                 | 132 (88.000)              |
| Male, n (%)                      | 15 (10.00)                  | 18 (12.00)                |
| Clinical manifestations          |                             |                           |
| Malar rash, n (%)                | 68 (45.3)                   | –                         |
| Discoid rash, n (%)              | 29 (19.3)                   | –                         |
| Photosensitivity, n (%)          | 58 (38.6)                   | –                         |
| Oral ulcers, n (%)               | 36 (0.24)                   | –                         |
| Arthritis, n (%)                 | 97 (64.7)                   | –                         |
| Serositis, n (%)                 | 15 (10.0)                   | –                         |
| Renal disorders, n (%)           | 75 (50.0)                   | –                         |
| Neurological disorders, n (%)    | 7 (4.6)                     | –                         |
| Hematological disorders, n (%)   | 102 (68)                    | –                         |
| Anti-DNA, n (%)                  | 72 (64.3)                   | –                         |
| Anti-Sm, n (%)                   | 50 (33.3)                   | –                         |
| Anti-Ro/SS-A, n (%)              | 32 (21.3)                   | –                         |
| Anti-La/SS-B, n (%)              | 17 (11.3)                   | –                         |

n, number; SLE, systemic lupus erythematosus.
the two groups, indicating that both the dominant and cumulative models are suitable for describing the genetic pattern of IL19 rs2243188 (Table 5).

**Synergy analysis of BCL2 and IL19**

Individuals carrying both the 195-bp BCL2 and 138-bp IL19 susceptibility alleles were found to be at a significantly higher risk of developing SLE than those with either susceptibility allele alone ($P=0.001$) (Table 6).

**Discussion**

SLE is a complex connective tissue disease whose specific cause is not clear, although multiple factors are involved in its development including genetics, the environment, infections, and drugs. Cytokines are a class of biologically active small molecule proteins that are produced and secreted by lymphocytes or monocytes. The abnormal activation of lymphocytes leads to the aberrant expression of a variety of autoantibodies and cytokines, resulting in immune

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**Table 2.** Comparison of the distributions of common BCL2 alleles between patients and controls [n (%)].

| Genotype (bp) | SLE   | Control | $\chi^2$ | P-value |
|--------------|-------|---------|----------|---------|
| 189          | 28 (18.7) | 35 (20.0) | 0.985 | 0.321 |
| 191          | 28 (18.7) | 6 (4.0)   | 16.055 | <0.001 |
| 193          | 2 (1.3)   | 22 (14.7) | 18.116 | <0.001 |
| 195          | 67 (44.7) | 45 (30.0) | 6.989  | 0.009  |
| 197          | 15 (10)   | 36 (24.0) | 10.418 | 0.001  |
| 199          | 4 (26.7)  | 5 (3.3)   | 0.108  | 0.743  |
| 201          | 23 (15.3) | 27 (18.0) | 0.384  | 0.535  |
| 203          | 3 (2.0)   | 9 (6.0)   | 3.125  | 0.077  |

SLE, systemic lupus erythematosus.

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**Table 3.** Comparison of the distributions of major BCL2 genotypes between patients and controls [n (%)].

| Genotype (bp) | SLE   | Control | $\chi^2$ | P-value |
|--------------|-------|---------|----------|---------|
| 195/191      | 38 (25.3) | 9 (6.0) | 21.218 | <0.001 |
| 195/193      | 17 (11.3) | 13 (8.7) | 0.593  | 0.441  |
| 195/195      | 21 (14.0) | 11 (7.3) | 3.498  | 0.061  |
| 195/197      | 13 (8.7)  | 11 (7.3) | 0.181  | 0.670  |
| 195/199      | 5 (3.3)   | 3 (2.0)  | 0.514  | 0.473  |
| 195/201      | 28 (18.7) | 27 (18.0) | 0.022  | 0.881  |
| 195/203      | 2 (1.3)   | 3 (2.0)  | 0.203  | 0.652  |

n, number; SLE, systemic lupus erythematosus.

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**Table 4.** Genotype distribution of the IL19 SNP rs2243188 between patients and controls [n (%)].

| Genotype | SLE   | Control | $\chi^2$ | P-value |
|----------|-------|---------|----------|---------|
| CC       | 13 (8.6) | 9 (6.0) | 32.14 | <0.001 |
| AA       | 72 (48.0) | 13 (8.7) |         |         |
| CA       | 65 (43.4) | 11 (7.3) |         |         |

n, number; SLE, systemic lupus erythematosus.
system disorders that play an important role in the pathogenesis and development of SLE.\textsuperscript{17}

Bcl-2 inhibits or delays a series of stimulation-induced apoptosis events.\textsuperscript{18} The survival time of B cells is prolonged in transgenic organisms overexpressing Bcl-2, which likely induces the production of a large number of autoantibodies and lupus-like glomerulonephritis.\textsuperscript{19} Bcl-2 itself is critical to B and T cell development and survival in healthy individuals, and its overexpression has been suggested to increase the survival of autoreactive cells and thus contribute to the pathogenesis of SLE.\textsuperscript{20} Clinical studies have also reported the overexpression of \textit{BCL2} in the lymphocytes of patients with SLE, especially those with active disease, indicating that their lymphocytes escape apoptosis and exist in a state of activation and proliferation, causing autoimmune system dysfunction.\textsuperscript{21}

Previous findings of the correlation between \textit{BCL2} polymorphisms and SLE susceptibility are inconsistent. In a study of Mexican Americans, Mheirann et al.\textsuperscript{22} proposed for the first time that a microsatellite polymorphism of \textit{BCL2} was related to SLE; Wu et al.\textsuperscript{5} showed a similar result in a Chinese family. Additionally, a full genome scan showed that the 18q21-q22 region (in which \textit{BCL2} is located) was associated with SLE.\textsuperscript{23} However, a case–control study by Johansson et al.\textsuperscript{24} and transmission imbalance analyses found no correlation in Mexican or Swedish SLE pedigrees, and no association was found in Caucasian\textsuperscript{25} and Italian\textsuperscript{26} populations. Komaki et al.\textsuperscript{27} showed that the first SNP at codon 43 of \textit{BCL2} is an A–G polymorphism, corresponding to a novel polymorphic (Ala43Thr; ACC → GCC) \textit{BCL2} allele. The frequency of 43Thr in the 57 patients with SLE investigated was 7.0%, which differed significantly from that of healthy controls (14.5%) (P < 0.01). Investigations of several other autoimmune diseases found similar results, indicating that \textit{BCL2} 43Thr may be involved in resistance to autoimmune diseases.

### Table 5. Analysis of the \textit{IL19} SNP rs2243188 genetic pattern between patients and controls [n (%)].

| Mode type          | Genotype | SLE   | Control | $\chi^2$ | P-value |
|--------------------|----------|-------|---------|----------|---------|
| Recessive Model    | CC       | 13 (8.6) | 15 (10.0) | 0.158 | 0.843   |
|                    | CA+AA    | 137 (91.4) | 135 (90.0) |       |         |
| Dominant pattern   | CC+CA    | 78 (72.0) | 36 (24.0) | 24.958 | 0.001   |
|                    | AA       | 72 (28.0) | 114 (76.0) |       |         |

\textit{n}, number; SLE, systemic lupus erythematosus.

### Table 6. Comparison of the synergistic effects of \textit{BCL2} and \textit{IL19} susceptibility alleles between patients and controls [n (%)].

| Genotype (bp) | SLE | Control | Odds ratio | 95% confidence interval | P-value |
|---------------|-----|---------|------------|------------------------|---------|
| \textit{IL19} 138/X, 138/138 | BCL2 195/Y, 195/195 | 54 (36.0) | 27 (18.0) | 2.562 | 1.503–4.369 | 0.001 |
|               | BCL2 Y/Y | 19 (12.7) | 28 (18.7) | 0.632 | 0.336–1.190 | 0.155 |
| \textit{IL19} X/X | BCL2 195/Y, 195/195 | 18 (12.0) | 15 (10.0) | 1.227 | 0.594–2.537 | 0.58  |
|               | BCL2 Y/Y | 3 (2.0) | 6 (4.0) | 0.49 | 0.120–1.996 | 0.319 |

\textit{X} and \textit{Y} refer to alleles other than the 195-bp \textit{BCL2} and 138-bp \textit{IL19} susceptibility alleles. \textit{n}, number; SLE, systemic lupus erythematosus; BCL2, B cell lymphoma 2; IL19, interleukin-19.
In the present study, we conducted genotyping of BCL2 microsatellites in SLE core families and healthy individuals in the Chinese population. The frequency distribution of BCL2 alleles in patients with SLE in the Chinese population differed significantly from that of Mexican American and Swedish populations. Because different ethnicities have different genetic backgrounds, we would expect a degree of allelic heterogeneity. Moreover, differences in experimental and analytical methods may lead to varied results.

IL19 is located on human chromosome 1q32 and is closely linked to IL10 as part of a gene cluster with IL20 and IL24. IL-19 binds IL-20Rα and IL-20Rβ to induce signal transducer and activator of transcription (STAT)-1 and STAT-3 activation. It also induces T helper type 2 cytokine secretion in vitro and increases tumor necrosis factor-α and IL-6 expression. In its dual pro-inflammatory and anti-inflammatory roles, it upregulates keratinocyte growth factor transcripts on CD8+ T cells in patients with psoriasis and is thought to contribute to the inflammatory process. Furthermore, elevated IL-19 levels are associated with increased production of many inflammatory cytokines, of which several are related to the mechanism of SLE. Zhang et al. found that serum levels of IL-19, IL-24, IL-26, IL-31, IL-32, and IL-36 in Chinese patients with SLE did not differ markedly from those of healthy controls, but these cytokines induce the abnormal expression of pro-inflammatory cytokines in SLE. Several lines of evidence have also implied a link between IL-19 and LN. In a mouse acute kidney injury model, mouse kidneys overexpressed IL-19 as well as the protein and mRNA of its receptor. After IL-19 treatment of renal epithelial M1 cells, transcripts of transforming growth factor-β1, monocyte chemotactic protein (MCP)-1, and IL-19, which are involved in the pathogenesis of LN, were all upregulated. Moreover, urine MCP-1 levels were significantly increased in patients with LN compared with non-LN patients.

In the present study, fluorescence-labeled satellite typing was performed on 150 patients with SLE and 150 healthy subjects, and logistic regression analysis of the synergistic effects of BCL2 and IL19 revealed significant differences in the distributions of major BCL2 genotypes and common alleles. The genotype distribution of the IL19 SNP rs2243188 was shown to be closely related to clinical symptoms of SLE, and individuals carrying both the 195-bp BCL2 and 138-bp IL19 susceptibility alleles found to be at higher risk of developing SLE than those carrying either allele alone.

Several limitations of our study should be considered. First, all of our patients were Chinese, and our findings should be interpreted while considering that association analyses of microsatellite and SNP markers did not support the involvement of BCL2 in SLE in Mexican and Swedish patients and their families. Second, our patients were at different stages of disease, and some were receiving treatment drugs that may have affected gene expression. Third, our sample size was small, so our results may not be widely representative. Moreover, this was a case–control study based on hospital data, and selection bias was inevitable. We did not perform a sample size calculation, and the limited number of participants may have affected the statistical significance of the results. Therefore, broader and more in-depth research on susceptibility to SLE should be carried out using genome-wide statistical association studies in the future.

**Conclusions**

This study provides compelling evidence that a BCL2 polymorphism and IL19 SNP rs2243188 are closely related to the
pathogenesis of SLE. These loci may directly participate in the development of SLE, or linkage disequilibrium in nearby susceptibility sites may occur to cause disease. The polymorphisms also have a synergistic effect on the susceptibility to SLE.

Author contributions
WJ-W and XC-W contributed equally to this paper. WJ-W and YS-F conceived and designed the experiments. WJ-W and XC-W performed the experiments. KP-Y analyzed the data. YS-F supervised the experiments. WJ-W wrote the paper. All authors read and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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