Association Study of a Proliferation-inducing Ligand, Spermatogenesis Associated 8, Platelet-derived Growth Factor Receptor-alpha, and POLB Polymorphisms with Systemic Lupus Erythematosus in Chinese Han Population

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Abstract

Background: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with complex genetic inheritance. This study was conducted to examine whether the association of a proliferation‑inducing ligand (APRIL), spermatogenesis associated 8 (SPATA8), platelet-derived growth factor receptor-alpha (PDGFRA), and DNA polymerase beta (POLB) with SLE can be replicated in a Chinese Han population.

Methods: Chinese SLE patients (n = 1247) and ethnically and geographically matched healthy controls (n = 1440) were genotyped for the APRIL, SPATA8, PDGFRA, and POLB single-nucleotide polymorphisms (SNPs), rs3803800, rs8023715, rs1364989, and rs12678588 using the Sequenom MassARRAY System.

Results: The Chinese Han SLE patients and controls had statistically similar frequencies of alleles and genotypes of four gene polymorphisms. Moreover, no association signal was detected on different genetic models (additive, dominant, and recessive, all, P > 0.05) or in SLE subgroups stratified by various clinical manifestations (all, P > 0.05).

Conclusions: Different genetic backgrounds from different ancestries and various populations may result in different genetic risk factors for SLE. We did not detect any significant association with SNPs of APRIL, SPATA8, PDGFRA, and POLB.

Key words: A Proliferation-inducing Ligand; Genetic Association; Spermatogenesis Associated 8; Systemic Lupus Erythematosus; Platelet-derived Growth Factor Receptor-alpha; POLB

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, inflammatory autoimmune disease capable of damaging multiple organs.[1] Although the etiology of SLE has not been fully elucidated, certain genetic factors have been implicated in its pathogenesis, clinical expression, and production of its characteristic autoantibodies.[2] The reported incidences of SLE in China and Europe are 31–70 cases and 7–71 cases per 100,000 individuals, respectively,[3,4] suggesting that its incidence varies by different ethnic groups. In recent years, several genome-wide association studies (GWASs) have been conducted using biological samples obtained from large cohorts of SLE patients and normal control cases to investigate the role of genetic factors in the development of SLE. During the course of these studies, >50 commonly occurring single-nucleotide polymorphisms (SNPs) were found to be associated with SLE, including human leukocyte antigen (HLA) regions HLA-DRB1-HLA-DQA1.[5]
HLA-DQB1-HLA-DQA2, as well as non-HLA genes (RasGRP3, STAT4, IRF5-TNPO3, ETS1, IKZF1, and TNFAIP3).

A proliferation-inducing ligand (APRIL, also called TNFSF13), a newly identified member of the tumor necrosis factor ligand family, is a Type II membrane binding protein of 250 amino acids. APRIL binds to two of three B-cell activating factor (BAFF) receptors (B-cell maturation antigen and transmembrane activator and CAML interactor [TACI]) and is supposed to have a regulatory role in B-cell proliferation. The treatment of lupus prone (NZB6W) F1 mice with a soluble TACI-immunoglobulin fusion protein (soluble decoy receptor for BAFF and APRIL) inhibits the development of proteinuria and prolongs survival of the animals. GWAS revealed linkages of the chromosomal regions 13q32, 17p12-q11, and 17p13 with SLE. These regions contain the genes encoding BlyS (13q32), APRIL (17p13), and TACI (17p11.2). These findings led us to consider APRIL as a strong candidate susceptibility gene to autoimmune disease.

Spermatogenesis associated 8 (SPATA8) is a protein coding gene. At present, a database of citations about SPATA8 gene is limited; however, recently, a GWAS of a European population with SLE showed an association between disease susceptibility and SPATA8. A genome-wide interaction study also showed that SPATA8 was associated with HDL level in Rotterdam study.

PDGF signaling pathways containing platelet-derived growth factor receptor-alpha (PDGFRα) and platelet-derived growth factor receptor-beta (PDGFRβ) act to promote local cell proliferation, synthesis of extracellular matrix, chemotaxis, and cytokine production and play a regulatory role in inflammation. Both PDGFRα and PDGFRβ are expressed in renal glomeruli and in the interstitium. Signaling through the PDGFRα pathway can activate interstitial and mesangial cells, which can lead to renal fibrosis and tubulointerstitial scarring. The most significant evidence of an association with lupus nephritis was observed with rs1364989, located 83 kb from PDGFRA.

POLB, which was localized to chromosome 8p11.2, encodes a DNA polymerase (Pol-β) that is involved in the repair of single-strand breaks as a part of the base excision and repair pathway. POLB gene mutation and overexpression have been reported in various cancers. In one recent study, a POLB Y265C/C mouse model developed an autoimmune pathology that strongly resembled SLE.

Further characterizing the heritability of SLE is challenging because of the large amount of genetic and phenotypic heterogeneity. Different genetic variations and molecular pathways may be of varying importance in different patients. This study was conducted to examine whether the association of APRIL, SPATA8, PDGFRA, and POLB with SLE can be replicated. To address these issues, we carried out a polymorphism of these SNPs and analyzed the association with SLE in Chinese Han.

**Results**

**Characterization of enrolled cases and statistical test of Hardy–Weinberg equilibrium**

The characteristics of enrolled cases are listed in Table 1. The age distribution between cases (34.7 ± 12.6)
and controls (39.3 ± 12.5) was not statistically significant (Mann–Whitney U-test, \( P = 0.84 \)), and the two groups showed balanced gender composition (female: male ratio was 10.9 and 10.7 in cases and controls, respectively). In addition, no deviation from HWE was detected for all SNPs in control population.

**Association between gene polymorphisms and systemic lupus erythematosus**

Genotype and allele frequencies for patients and controls of the four SNPs in HWE are shown in Table 2. There was no significant difference in the genotype frequencies of both SNPs (all, \( P > 0.05 \)), and similar results were also observed in the comparison of allele frequency. Even though the \( P = 0.04 \) in the allele frequency of SPAT8 (rs8023715), it does not reach the preset Bonferroni correction of the \( P \) value. Based on three genetic models (additive, dominant, and recessive), genotype distributions for both SNPs were tested [Table 3], and no significant difference was detected in any genetic models.

**Correlation between systemic lupus erythematosus single-nucleotide polymorphisms and the subphenotypes of systemic lupus erythematosus**

We also looked for associations between the SNPs in HWE and different clinical manifestations of SLE. Patients were stratified based on seven subphenotypes of SLE including nephritis, anti-SSA/B antibodies, RNP, anti-dsDNA antibody, anti-Sm antibody, and low complements. In our SLE sample, most of the patients had manifestation of anti-SSA antibody (60.6%) and low complement (59.0%), and fewer patients were positive for anti-SSB antibody (11.9%). The results of subphenotype-based association studies are listed in Table 4, and no SNP was observed to be associated with the seven clinical manifestations (all, \( P > 0.05 \)).

**DISCUSSION**

The major aim of this study was to determine whether previously identified SLE susceptibility SNPs were also associated with SLE in northern Han Chinese. We observed some significant differences from the previous findings in Caucasian Europeans. In this study, all SNPs we selected have negative association with the SLE, and in subphenotype analysis, all SNPs failed to achieve positive associations with any clinical manifestation.

APRIL and BAFF are both members of the TNF ligand superfamily. Chu et al.\[^{23}\] showed a strong correlation between disease activity of SLE and the level of BAFF and APRIL mRNA expression in CD19+ B and plasma cells. Stohl\[^{24}\] reported that APRIL may enhance the longevity of autoantibody-producing plasma cells in an SLE host, and its neutralization may, therefore, result in decreased production of autoantibodies. In a previous report, Treamtrakanpon et al.\[^{25}\] revealed that serum levels of APRIL were higher in the patients with proteinuria than in others without proteinuria which supported the pivotal role for APRIL in lupus nephritis patients. Recently, Koyama et al.\[^{26}\] identified two novel polymorphisms at the APRIL codons 67 in exon 1 (rs11552708) and 96 in exon 2 (rs3803800) in a Japanese population. These two SNPs were not significant linkage disequilibrium (\( r^2 = 0.175 \)). Moreover, Lee et al.\[^{27}\] reported that these two SNPs were not associated with SLE in European-American population. Our study showed that it was consistent with European-American population.

**Table 1: Clinical symptoms of SLE patients stratified information, \( n = 1247 \)**

| Characteristics       | Positive* (%) | Negative* (%) |
|-----------------------|---------------|---------------|
| Lupus nephritis       | 650 (52.1)    | 597 (47.9)    |
| Anti-Sm antibodies    | 315 (25.3)    | 932 (74.7)    |
| Anti-SSA antibodies   | 756 (60.6)    | 491 (39.4)    |
| Anti-SSB antibodies   | 149 (11.9)    | 1098 (88.1)   |
| Anti-RNP antibodies   | 491 (39.4)    | 756 (60.6)    |
| Anti-dsDNA antibodies | 589 (47.2)    | 658 (52.8)    |
| Low complement        | 736 (59.0)    | 511 (41.0)    |

*Patients positive for a certain phenotype; †Patients negative for a certain phenotype. SLE: Systemic lupus erythematosus.

**Table 2: SNPs associated with 1247 SLE patients and 1440 healthy controls**

| SNPs/Location   | Groups | Genotype frequency (%) | \( \chi^2 \) | \( P \) | Allele frequency (%) | \( P \) | OR (95% CI) |
|-----------------|--------|------------------------|-------------|--------|----------------------|--------|------------|
| rs3803800 (exon)| Case   | AA 132 (10.6)          | NA          |        | A 862 (35.1)         | 0.91   | 1.04 (0.54–2.01) |
|                 |        | AG 539 (43.2)          | NA          |        | G 1655 (67.3)        |        |             |
|                 |        | GG 558 (44.7)          | NA          |        |                      |        |             |
|                 | Control| AA 140 (9.7)           | NA          |        | A 878 (30.7)         | 0.84   |             |
|                 |        | AG 598 (41.5)          | NA          |        | G 1980 (69.3)        |        |             |
|                 |        | GG 691 (48.0)          | NA          |        |                      |        |             |
| rs8023715 (intergenic region) | Case | AA 4 (0.3) | 97 (7.8) | 1126 (90.3) | 3.90 | 0.14 | A 105 (4.3) | 155 (5.5) | 0.04 | 0.77 (0.60–0.99) |
|                 |        | AC 139 (9.7)           | 1274 (86.6) | 0.04 | C 2349 (95.7)        |        |             |
|                 | Control| TT 3 (0.2)             | 127 (10.2) | 1095 (87.8) | 1.14 | 0.57 | T 133 (5.4) | 156 (5.4) | 0.98 | 1.00 (0.79–1.27) |
|                 |        | TC 127 (9.9)           | 1284 (89.2) | 0.54 | C 2317 (94.6)        |        |             |
|                 |        | CC 1284 (89.2)         | NA          |        |                      |        |             |
| rs1364989 (intronic) | Case | AA 7 (0.5) | 142 (9.9) | 1284 (89.2) | 2.03 | 0.03 | A 17 (0.7) | 19 (0.7) | 0.54 | 0.96 (0.84–1.09) |
|                 |        | AG 1410 (99.3)         | NA          |        | A 2441 (99.3)        |        |             |
|                 | Control| 0 (0)                  | 17 (1.4) | 1212 (97.2) | 2.36 | 0.36 | G 2839 (99.3) |        |        |             |
| rs12678588 (exon) | Case | AA 0 (0) | 19 (1.3) | 1410 (97.9) | 0.04 | 0.96 | A 19 (0.7) | 2839 (99.3) |        |             |

NA: Not applicable; SNPs: Single-nucleotide polymorphisms; OR: Odds ratio; CI: Confidence interval; SLE: Systemic lupus erythematosus.
Rs8023715 of SPATA8 is an A/C single-nucleotide variation on human chromosome 15, and its function was not clearly identified. It was reported that it was associated with SLE in European. However, in our study, the result showed that the SNP in SPATA8 gene has negative association with SLE, which was different from previous studies. After analyzing the allele frequency data from HapMap phase 3, there was no obvious difference in Chinese, European, and African populations (minor allele frequency A: 7%, 9%, and 10%, respectively).

Overproduction of PDGF gene is known to be increased in kidney tissue from patients with proliferative forms of GN, including LN, IgA nephropathy, and Henoch–Schönlein purpura in human. Chung et al. reported that PDGFRA gene showed a significant enrichment of LN regulated transcripts with 12 of 79 molecules being differentially expressed using ingenuity pathway analysis; meanwhile, the study confirmed that PDGFRA was the main node of LN gene using GePS (Gene Expression Pattern Scanner, http://bioinf.xmu.edu.cn/software/geps/geps.php) software, the study also showed that rs1364989 in PDGFRA had an association with LN in European. These data suggest that PDGFRA gene may mediate the pathogenesis of LN and may influence the development of LN in human. Therefore, we selected rs1364989 in our analysis of northern Han Chinese samples; however, these associations were not observed in the present study. We inferred that the allele frequency differences of rs1364989 in Chinese, European, and African populations might be the reason for the inconsistencies between the association signals in these populations (minor allele frequency T: 5%, 22%, and 49%, respectively).

A replication study of a previous GWAS suggested that an SNP linked to the POLB gene is associated with SLE. Within the 33 kb POLB gene, as many as 567 SNPs have been identified. However, only 34 SNPs are in or near the coding region (22 are found in exons), and only two have

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**Table 3: Genetic models and statistical analysis**

| SNPs       | Additive model |         |         | Dominant model |         |         | Recessive model |         |
|------------|----------------|---------|---------|----------------|---------|---------|----------------|---------|
|            |                | P       | OR (95% CI) | P       | OR (95% CI) | P       | OR (95% CI) |
| rs3803800  | 0.91           | 1.04 (0.54–2.01) | 0.91    | 1.04 (0.54–2.01) | NA     | NA     |
| rs8023715  | 0.05           | 0.78 (0.61–1.00) | 0.06    | 0.77 (0.59–1.01) | 0.37   | 0.58 (0.17–1.92) |
| rs1364989  | 0.98           | 1.00 (0.79–1.26) | 0.86    | 1.02 (0.80–1.31) | 0.32   | 0.50 (0.13–1.94) |
| rs12678588 | 0.54           | 0.96 (0.84–1.10) | 0.31    | 0.92 (0.79–1.08) | 0.50   | 1.13 (0.79–1.63) |

NA: Not applicable; OR: Odds ratio; CI: Confidence interval; SNPs: Single-nucleotide polymorphisms.

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**Table 4: Association of 4 SNPs with SLE analyzed by subphenotype stratification**

| Subphenotypes | Comparison | rs3803800 (APRIL) | rs8023715 (SPATA8) | rs1364989 (PDGFRA) | rs12678588 (POLB) |
|---------------|------------|-------------------|--------------------|--------------------|--------------------|
|               |            | P      | OR (95% CI) | P      | OR (95% CI) | P      | OR (95% CI) | P      | OR (95% CI) |
| Lupus nephritis |           | 0.67  | 0.81 (0.31–2.11) | 0.74 | 0.94 (0.63–1.39) | 0.21 | 0.80 (0.56–1.13) | 0.26 | 1.12 (0.92–1.36) |
| Anti-SSA      |            | 0.88  | 0.94 (0.41–2.15) | 0.07 | 0.75 (0.54–1.03) | 0.45 | 0.89 (0.66–1.20) | 0.88 | 1.01 (0.86–1.19) |
| Anti-SSB      |            | 0.73  | 1.15 (0.52–2.55) | 0.17 | 0.80 (0.58–1.10) | 0.46 | 1.11 (0.83–1.49) | 0.24 | 0.90 (0.77–1.07) |
| Anti-RNP      |            | 0.89  | 0.93 (0.35–2.46) | 0.08 | 1.45 (0.95–2.21) | 0.63 | 1.09 (0.76–1.57) | 0.29 | 1.11 (0.91–1.36) |
| Anti-Sm       |            | 0.98  | 1.01 (0.47–2.18) | 0.38 | 0.88 (0.66–1.17) | 0.82 | 1.03 (0.78–1.36) | 0.99 | 1.00 (0.86–1.17) |
| Anti-dsDNA    |            | 0.86  | 1.08 (0.45–2.59) | 0.01 | 0.61 (0.41–0.89) | 0.73 | 0.94 (0.68–1.31) | 0.24 | 0.90 (0.75–1.08) |
| Low complement |           | 0.96  | 0.97 (0.22–4.25) | 0.18 | 1.43 (0.84–2.45) | 0.77 | 0.92 (0.53–1.60) | 0.97 | 1.01 (0.75–1.35) |
| rs3803800 (APRIL) |            | 0.01  | 3.64 (1.28–10.44) | 0.54 | 1.13 (0.76–1.68) | 0.61 | 1.10 (0.77–1.56) | 0.63 | 1.05 (0.86–1.28) |
| rs8023715 (SPATA8) |           | 0.09  | 1.85 (0.89–3.82) | 0.27 | 0.83 (0.59–1.16) | 0.75 | 1.05 (0.77–1.45) | 0.89 | 0.99 (0.83–1.18) |

* SLE patients positive for a certain subphenotype; † SLE patients negative for a certain subphenotype; Healthy controls; ‡ Chi-square test for allele frequency comparisons between stratified groups. OR: Odds ratio; CI: Confidence interval; SLE: Systemic lupus erythematosus; SNPs: Single-nucleotide polymorphisms; APRIL: A proliferation-inducing ligand; SPATA8: Spermatogenesis associated 8; PDGFRA: Platelet-derived growth factor receptor-alpha; POLB: DNA polymerase beta.
been confirmed in larger cohorts. These two germline POLB mutants (R137Q; rs12678588 and P242R; rs3136797) have been reported to be present in as much as 0.6% and 2.4% of the human population, respectively. An earlier study on the Pol-β (R137Q) mutant (rs12678588) suggested that the R137Q mutation impairs function of the purified protein. Unfortunately, our current study failed to confirm association of these SNPs with SLE development.

We did not detect any significant association with SNPs of APRIL, SPATA8, PDGFRA, and POLB. There are several reasons to explain the difference between Chinese and European. First, the genetic basis of SLE is complex since numerous genes are implicated and the magnitude of the effect of each gene is quite small, which suggests that the interaction or the additive effect of several genes is necessary to reach the threshold for the development of SLE. Second, we only assessed one SNP each for four genes. The results obtained by this study may not completely represent the association between these SNPs and SLE risk. Third, even if the differences between cases and controls are large, the fact that some genes are associated with specific lupus manifestations rather than with disease susceptibility. Finally, ethnic diversity also has an important role in the heterogeneity of the genetic associations given that a sizable number of them do not cross racial barriers.

In conclusion, genetic predisposition in SLE is complex. It is important to underscore that ethnicity has been shown to exert a significant role in both disease susceptibility and disease expression. Understanding population differences in genetic susceptibility for a complex disease like SLE will improve our understanding of the disease and improve clinical intervention. Future large-scale mapping and sequencing in this region will help clarify true causal genomic elements.

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Conflicts of interest
There are no conflicts of interest.

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