The ZNF76 rs10947540 polymorphism associated with systemic lupus erythematosus risk in Chinese populations

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Systemic lupus erythematosus (SLE) is a typical autoimmune disease with a strong genetic disposition. Genetic studies have revealed that single-nucleotide polymorphisms (SNPs) in zinc finger protein (ZNF)-coding genes are associated with susceptibility to autoimmune diseases, including SLE. The objective of the current study was to evaluate the correlation between ZNF76 gene polymorphisms and SLE risk in Chinese populations. A total of 2801 individuals (1493 cases and 1308 controls) of Chinese Han origin were included in this two-stage genetic association study. The expression of ZNF76 was evaluated, and integrated bioinformatic analysis was also conducted. The results showed that 28 SNPs were associated with SLE susceptibility in the GWAS cohort, and the association of rs10947540 was successfully replicated in the independent replication cohort (P_replication = 1.60 × 10−2, OR 1.19, 95% CI 1.03–1.37). After meta-analysis, the association between rs10947540 and SLE was pronounced (Pmeta = 9.62 × 10−6, OR 1.29, 95% CI 1.15–1.44). Stratified analysis suggested that ZNF76 rs10947540 C carriers were more likely to develop relatively high levels of serum creatinine (Scr) than noncarriers (CC + CT vs. TT, p = 9.94 × 10−4). The bioinformatic analysis revealed that ZNF76 rs10947540 was annotated as an eQTL and that rs10947540 was correlated with decreased expression of ZNF76. Remarkably, significantly reduced expression of ZNF76 was confirmed by expression data from both our laboratory and an array-based expression database. Taken together, these results suggest that ZNF76 rs10947540 is a possible susceptibility factor associated with SLE susceptibility. The mechanism underlying the relationship between ZNF76 and SLE pathogenesis still requires further investigation.

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ZNF76 is a novel transcriptional repressor targeting TATA-binding protein that has been shown to have an inhibitory effect on p53 activity by reporter assays and on endogenous target gene expression. Integrated analysis of three original datasets, GSE72509, GSE20864, and GSE39088, from the Gene Expression Omnibus (GEO) database identified that the p53 signalling pathway may be implicated in SLE pathogenesis. Considering both genetic clues concerning variants in zinc finger protein-coding genes contributing to susceptibility to autoimmune diseases, including SLE, and the biological functions of ZNF76, we aimed to explore the role of ZNF76 in the pathogenesis of SLE.

Based on a previous SLE GWAS, we first replicated the tag SNP in our cohort to confirm the genetic association between ZNF76 variants and SLE susceptibility. By using a public database, we explored the functional role of ZNF76 rs10947540 and the differential expression of ZNF76, which was also validated by expression data from our centre.

Methods

Study populations. The replication cohort contained 1003 SLE patients and 815 healthy controls from the Henan population in the middle of China. All the patients were diagnosed by at least two experienced physicians according to the revised criteria for the classification of SLE from the American College of Rheumatology (ACR)11. Clinical data were retrospectively collected at the time of diagnosis. Written informed consent was obtained from each participant. This investigation was conducted according to the Declaration of Helsinki. The study was approved by the Medical Ethics Committee of Zhengzhou University First Hospital (2019-KY-134).

SNP selection and genotyping. We focused on the 10-kb upstream and downstream regions of the ZNF76 gene ranging from 35,217,512—35,273,762 on chromosome 6. Thirty-seven SNPs were covered by the ImmunoChip used in the GWAS and are listed in supplementary Table 1. Genetic association results were obtained from a previous publication12.

A total of 28 SNPs associated with SLE susceptibility were identified in the GWAS cohort (supplementary Table 1)12. Five intronic polymorphisms within ZNF76, rs10947540, rs9394289, rs2267663, rs1894650, and rs9366883, were the top signals ($p = 1.31 \times 10^{-5}$) and were highly linked ($D' = 1.0, r^2 = 1.0$, Fig. 1) after analysing genotype data from 103 Chinese Han Beijing (CHB) individuals from the 1000 Genomes Project (Fig. 1). Further, rs10947540 was chosen as the tag SNP and was validated in the replication cohort. The Sequenom MassARRAY platform (Sequenom, Inc., San Diego, California, USA) was used for genotyping the replication cohort, and the genotyping yield was 99.5%.

Rigorous quality control of the GWAS cohort was performed previously and provided in a previous publication12. For the replication cohort, the missing genotyping rate of rs10947540 was 0.50% in the cases vs. 0.37% in the controls, and the Hardy–Weinberg equilibrium was $p = 0.86$ in the cases vs. $p = 0.46$ in the controls.

Bioinformatic and differential gene expression analyses. Regulatory functions were annotated with rSNPBase13. The summarized expression quantitative trait loci (eQTLs) of rs10947540 were obtained from HaploReg v4.114.

Allele-dependent gene expression was determined by the combined use of the ArrayExpress Archive database (http://www.ebi.ac.uk/arrayexpress) and Ensembl (http://www.ensembl.org). Differential gene expression data for ZNF76, DEF6, and TAF11 was derived from both our in-house test and the E-GEOD-50772 project from the ArrayExpress Archive database15. The E-GEOD-50772 project was conducted with the A-AFFY-44-Affymetrix GeneChip Human Genome U133 Plus 2.0 with RNA from peripheral blood mononuclear cells (PBMCs)15.

Our expression analysis was performed with RNA from whole blood. The cDNA library was prepared according to the previously published protocol16 and sequenced with PE150 (Illumina, San Diego, California, USA). Clean reads were obtained after filtering out reads containing poly-N, sequencing adapters, and low-quality reads. The remaining clean reads were mapped to the reference genome using Hisat2 software. The expression levels were assessed based on the FPKM (Fragments Per Kilobase of transcript sequence per Millions base pairs sequenced) value.

Statistical analysis. Hardy–Weinberg equilibrium (HWE) among controls was assessed by the goodness-of-fit $\chi^2$ test. Allelic association analyses of SLE patients and healthy controls were performed using the chi-square test. The combined result for meta-analysis was from Cochran–Mantel–Haenszel statistics. Genotype-phenotype association analysis was conducted using the chi-square test for categorical variables and Student's t-test for continuous variables. Spearman's coefficient was calculated to determine correlations in allele-dependent gene expression analysis. The differences in ZNF76, DEF6, and TAF11 expression between SLE patients and healthy controls were tested using Student's t-test. Statistical analyses were implemented with SPSS 13.0 software. All results with a two-tailed $p < 0.05$ were considered statistically significant.

Ethics approval. The study was approved by the Medical Ethics Committee of Zhengzhou University First Hospital (2019-KY-134).

Consent to participate. The informed consent was obtained from all participants and/or their legal guardians.
Result

Association of ZNF76 gene polymorphisms with susceptibility to SLE. ZNF76 rs10947540 was selected as the tag SNP, and the association with SLE was successfully replicated ($p = 1.60 \times 10^{-2}$, OR 1.19, 95% CI 1.03–1.37) in a larger cohort with 1003 SLE patients and 815 healthy controls (Table 1). After meta-analysis of both the GWAS cohort from the GWAS and our replication cohort, the association between rs10947540 and SLE was pronounced ($P_{meta} = 9.62 \times 10^{-6}$, OR 1.29, 95% CI 1.15–1.44).

Demographics of SLE patients with three rs10947540 genotypes. Nine hundred ninety-eight SLE patients were successfully genotyped for ZNF76 rs10947540 and enrolled for clinical association analysis (Table 2). There were trends toward higher incidences of malar rash, discoid rash, photosensitivity, arthritis, serositis, haematological disorder, anti-dsDNA antibodies, and anti-Sm antibodies (without reaching statistical significance) in patients with the risk C allele than in the other patients. Notably, the SLE patients carrying the risk C allele showed significantly higher levels of serum creatinine (Scr) (CC + CT vs. TT, $p = 9.94 \times 10^{-4}$).

Bioinformatic analysis. ZNF76 rs10947540 was predicted to be a potential regulatory SNP by rSNPBase. Experimentally supported regulatory elements from ENCODE and other data resources showed that ZNF76 rs10947540 was in LD with other regulatory SNPs ($r^2 > 0.8$) and had potential distal regulation, RNA-binding.

### Table 1. Association of ZNF76 polymorphisms with systemic lupus erythematosus susceptibility.

| SNP       | Minor allele | MAF (%) | $P$   | OR (95% CI) | MAF (%) | $P$   | OR (95% CI) | $P$   | OR (95% CI) |
|-----------|--------------|---------|-------|-------------|---------|-------|-------------|-------|-------------|
| rs10947540 | C            | 39.6/30.2 | $1.3 \times 10^{-5}$ | $1.51$ (1.25–1.82) | 33.6/29.9 | $1.6 \times 10^{-2}$ | $1.19$ (1.03–1.37) | $9.62 \times 10^{-6}$ | $1.29$ (1.15–1.44) |

Table 1. Association of ZNF76 polymorphisms with systemic lupus erythematosus susceptibility. SNP Single nucleotide polymorphism, MAF minor allele frequency, OR odds ratio, CI confidence interval.
protein-mediated regulation, and an eQTL effect. Table 3 shows that rs10947540 was correlated with the expression of \(TCP11\), \(SCUBE3\), \(DEF6\), and \(ZNF76\) in certain tissues.

The GTEx Portal provides comprehensive tissue-specific gene expression and regulation data. We inferred from GTEx that rs10947540 is an eQTL (Fig. 2) associated with the expression of 7 genes (\(DEF6\), \(ZNF76\), \(PPARD\), \(SCUBE3\), \(RPL10A\), \(TCP11\), and \(TAF11\)) in 27 tissues (supplementary Table 2). Individuals carrying the risk C allele had lower expression of \(DEF6\) (\(p = 1.1 \times 10^{-49}\)) and \(ZNF76\) (\(p = 1.1 \times 10^{-19}\)) in whole blood samples (Fig. 3A).

Furthermore, we validated the eQTL effects in 488 individuals from HapMap projections. Individuals carrying the homozygous CC risk allele showed lower levels of \(ZNF76\) and \(DEF6\) expression and higher levels of \(TCP11\) expression than other patients (Fig. 3B). There was no correlation between the \(SCUBE3\) expression level and rs10947540 genotypes, which might be due to tissue-specific expression.

Reduced level of ZNF76 was observed in SLE. Considering the eQTL effect of rs10947540, we recruited 75 SLE patients and 24 healthy controls to ascertain whether \(ZNF76\) is differentially expressed. In accordance with the association of the risk C allele with lower levels of gene expression, our expression data for whole blood showed that lower levels of \(ZNF76\) expression were observed in the patients with SLE (Fig. 4A). Moreover, mRNA expression data from the E-GEOD-50772 project were consistent with our finding that the \(ZNF76\) expression in peripheral blood mononuclear cells from 61 SLE patients was significantly lower than that in PBMCs from 20 healthy controls (Fig. 4B).

Associated with rs10947540 in whole blood, we perform additional gene expression for \(DEF6\) and \(TAF11\). The expression of \(TAF11\) were significantly lower in SLE patients comparing with healthy controls both in our cohort and E-GEOD-50772 project. However, there were no difference in \(DEF6\) expression between SLE patients and healthy controls.

### Table 2. Prevalence of SLE clinical phenotypes between \(ZNF76\) rs10947540 polymorphisms in the replication cohort. \(Scr\) serum creatinine, \(24\ h\ UTP\) 24-h urinary protein, \(SLEDAI\) systemic lupus erythematosus disease activity index. *The \(p\)-value of \(Scr\) after adjusted for sex and age.

| Clinical Phenotypes | CC + CT (n = 557) | TT (n = 441) | \(p\)-value |
|---------------------|-------------------|--------------|-------------|
| Onset age (years, mean ± SD) | 31 ± 13 | 32 ± 13 | 0.140 |
| Gender (male, %) | 25 (5.7) | 46 (8.3) | 0.114 |
| Malar rash (+, %) | 142 (25.5) | 109 (24.7) | 0.779 |
| Discoid rash (+, %) | 5 (0.9) | 2 (0.5) | 0.404 |
| Photosensitivity (+, %) | 27 (4.8) | 15 (3.4) | 0.259 |
| Oral ulcers (+, %) | 40 (7.2) | 32 (7.3) | 0.964 |
| Arthritis (+, %) | 160 (28.7) | 118 (26.8) | 0.491 |
| Serositis (+, %) | 53 (9.5) | 30 (6.8) | 0.123 |
| Renal disorder Scr (μmol/L, mean ± SD) | 56 (48–71) | 54 (46–64) | 9.94 \( \times 10^{-4}\) (4.29 \( \times 10^{-5}\)a) |
| 24 h UTP (grams, mean ± SD) | 2.8 ± 9.1 | 2.1 ± 2.8 | 0.363 |
| Neurological disorder (+, %) | 17 (3.1) | 18 (4.1) | 0.380 |
| Hematological disorder (+, %) | 308 (56.3) | 233 (54.8) | 0.644 |
| Immunological disorder Anti-dsDNA antibodies (+, %) | 324 (64) | 245 (62) | 0.536 |
| Anti-Sm antibodies (+, %) | 83 (19.4) | 49 (15.1) | 0.119 |
| SLEDAI (mean ± SD) | 4 ± 4.0 | 4 ± 4.2 | 0.741 |

### Table 3. The eQTL effect of rs10947540 in multiple tissues by HaploReg v4.1.

| Tissues | Correlated genes | \(P\)-value |
|---------|------------------|-------------|
| Adipose Visceral Omentum | \(TCP11\) | \(1.52 \times 10^{-4}\) |
| Cells Transformed fibroblasts | \(SCUBE3\) | \(1.78 \times 10^{-1}\) |
| Nerve Tibial | \(DEF6\) | \(2.61 \times 10^{-4}\) |
| Skin Sun Exposed Lower leg | \(TCP11\) | \(2.05 \times 10^{-7}\) |
| Whole Blood | \(DEF6\) | \(1.95 \times 10^{-10}\) |
| Whole Blood | \(ZNF76\) | \(5.16 \times 10^{-9}\) |
| Lymphoblastoid EUR exomlevel | \(ENSG00000023892.8\) | \(1.42 \times 10^{-9}\) |
| Lymphoblastoid EUR exomlevel | \(ENSG00000023892.8\) | \(8.14 \times 10^{-4}\) |
| Lymphoblastoid EUR genelevel | \(DEF6\) | \(2.12 \times 10^{-9}\) |
| Whole Blood | \(DEF6\) | \(2.10 \times 10^{-12}\) |
| Whole Blood | \(ZNF76\) | \(2.45 \times 10^{-9}\) |
| Prepouch ileum | \(ZNF76\) | \(1.79 \times 10^{-20}\) |
Discussion

To determine whether SNPs in the ZNF76 gene predispose patients to SLE, we conducted a genetic replication of a previous GWAS genetic association result in an independent Chinese Han population. Our results showed that rs10947540 in ZNF76 predisposed patients to susceptibility to SLE. In the stratified analysis, we found that patients carrying the risk C allele (CC + CT genotypes) had a more evident risk and higher Scr levels. ZNF76, a novel transcriptional repressor targeting TATA-binding protein, has a strong inhibitory effect on p53 in various cell lines, including the HeLa, U2OS, MCF-7, and H1299 cell lines. Expression data from both our laboratory and the ArrayExpress Archive database demonstrated that the expression of ZNF76 was lower in patients with SLE than in healthy controls. P53 might be deregulated by the reduced expression of ZNF76. The presence of autoantibodies, increased cell apoptosis, and overactivation of type I IFN signalling pathways are

Figure 2. ZNF76 rs10947540 is an QTL locus. The quantitative trait locus in ZNF76 were generated by GTEx Locus Browser. ZNF76 rs10947540 was had eQTL and sQTL effects in multiple tissues.
Figure 3. The integrated expression and genotypic analysis of ZNF76 rs10947540. (A) The violin plot for expression of DEF6, ZNF76, and TAF11 in whole blood were obtained from GTEx database. (B) The correlation between ZNF76, DEF6, TCP11, and SCUBE3 and rs10947540 genotypes were adopted in E-MTAB-264 and the significances were tested by spearman’s correlation coefficient. The boxplot was generated via boxplot in SPSS.
prominent characteristics of SLE. In patients with SLE, elevated levels of p53 are detected in fibroblasts, bone marrow-derived mesenchymal stem cells, peripheral blood mononuclear cells, and renal tissues; they are also found in the skin of discoid lupus erythematosus patients. Researchers have reported that increased apoptosis is associated with p53 upregulation in p21-/- lupus mice. Moreover, p53 activation in SLE patients may stimulate type I IFN activity, promoting innate immune signalling directly. The production of autoantibodies requires p53 in B6/lpr lupus mice. We hypothesized that the reduced expression of ZNF76 promoted the pathogenesis of SLE, which might be due to deregulation of p53.

DEF6 is required for maintaining T cell effector functions and lymphocyte homeostasis and preventing systemic autoimmunity. Mice deficient in DEF6 can spontaneously develop a lupus-like syndrome with increased levels of autoantibodies and glomerulonephritis. The bioinformatic analysis revealed that ZNF76 rs10947540 was annotated as an eQTL associated with the expression of DEF6. Furthermore, genotyping and expression data from a HapMap population confirmed that the risk allele of rs10947540 was correlated with decreased expression of DEF6. We could not rule out the possibility that rs10947540 might promote the development of SLE by affecting DEF6 expression. ZNF76 functions as a transcriptional repressor. Whether the reduced expression of DEF6 was due to the regulation of ZNF76 remains to be elucidated.

The risk allele was associated with decreased ZNF76 expression levels according to data for individuals from the GTEx database and the expression data of HapMap3 projections. However, the data from the GTEx database and the expression data of HapMap3 projections were from healthy individuals. Thus, a limitation of this study was that we lacked data from SLE patients to explore the association between the risk allele and ZNF76 expression.

Our present study demonstrates that the rs10947540 polymorphism of the ZNF76 gene is a possible susceptibility factor associated with SLE susceptibility. The mechanism underlying the association between ZNF76 and the pathogenesis of SLE still requires further investigation.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions
Conceived and designed the experiment: Y.-Y.Q., Z.-Z.Z.; Performed the experiments: Y.-Y.Q., Y.C., X.-R.L., Y.-F.Z. and X.-H.N.; Analyzed the data: Y.-Y.Q., H.L., X.-Y.W., Y.-L.Z., and X.-X.Z.; Interpretation of the findings: Y.-Y.Q., H.L., Y.C. and Z.-Z.Z.; All the authors contributed to writing the manuscript.

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